Papers and Originals

Prevalence Rates of Uterine Cervical Carcinoma in situ for Women Using the Diaphragm or Contraceptive Oral Steroids*

MYRON R. MELAMED,† M.D.; LEOPOLD G. KOSS,† M.D.; BETTY J. FLEHINGER,‡ PH.D
RICHARD P. KELISKY,‡ PH.D.; HILLIARD DUBROW,§ M.D.

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Summary: Study of the prevalence rates of uterine cervical carcinoma in situ among women attending centres of Planned Parenthood of New York City, Inc., showed a small but statistically significant difference between the population choosing and using the diaphragm and the population choosing and using oral steroids for contraception. This can be attributed either to a decreased prevalence rate for women using the diaphragm or to an increased rate for women using oral steroids. The reason for the difference is not apparent from these data.

Introduction

In the autumn of 1965 a systematic long-range study of uterine cervical carcinoma in women using contraceptives was begun by Planned Parenthood of New York City, Inc., in conjunction with the Memorial Hospital for Cancer and Allied Diseases and the Sloan-Kettering Institute for Cancer Research. The study was designed primarily to determine whether various forms of contraceptives exert any influence on the development of cervical carcinoma. Two major statistical evaluations were proposed. The first, based on prevalence rates of the disease as found in an initial survey, was to compare matched populations of women who had been using the diaphragm with women using oral steroids. The second was planned as an incidence study of cervical carcinoma and related epithelial abnormalities as they develop in matched populations that are initially found to be free of the disease and are using the diaphragm, an intrauterine device, or oral steroids. The study of incidence rates will require several more years before it is complete. This report is concerned with an analysis of the prevalence rates.

Data Collection

The prevalence rates are for clinically occult cervical carcinomas and, except for a single case, they were all carcinomas in situ or carcinomas in situ with micofocal invasion. They were detected by cytology and confirmed by cervical biopsy or conization. Overt carcinoma of the uterine cervix was not found in this population, probably because of three factors: (1) this is a generally young population who would not be expected to have advanced disease, (2) the virtual absence of women with advanced cervical carcinoma probably reflects the effect of cancer screening programmes on the general population attending many different health facilities in New York City, and (3) it is probable that women with symptoms seek medical attention at hospitals or physicians' offices and do not think of Planned Parenthood centres as a treatment facility.

Routine annual examinations of cervical and vaginal cytology specimens were begun on all women at the onset of this study in October 1965, and the initial cytological screening was completed by July 1967. Previous to that cytological screening at Planned Parenthood centres had been performed routinely only for those women who wished to wear an intrauterine device. For this reason the analysis of prevalence rate data could not include the latter group. Only those women using the diaphragm and those using oral steroids for contraception were compared.

Collection of Cytology Specimens

The cytology specimens were obtained with cotton-tipped applicators, one from the cervix and endocervix and another from the vaginal pool; each was smeared on a separate glass slide and both slides were fixed immediately in 95% ethyl alcohol. The slides were taken by messenger to the Memorial Hospital, where they were stained, screened, and evaluated under the direction of two of us (M. R. M. and L. G. K.). Reports of the examination were mailed back to the centre.

Collection of Clinical Data

Clinical data necessary for this study, including a detailed record of the contraceptive method(s) used, were taken from each woman's chart at the Planned Parenthood centre when the cytology specimen was collected. In the case of new patients this information was contained in answers to specific questions on an initial history form that was filled in by trained interviewers who see each new applicant. This form also contains the examining physician's notes and prescription or recommendation, and a carbon copy accompanies the cytology specimen.

In the case of women who had been attending the centre before the start of the study an abstract was prepared from their chart and from a special supplemental question form filled in by the interviewer when the first cytology specimen was taken. For all of the women subsequent cytology specimens were always accompanied by a carbon copy of the interval notes that had been recorded in the chart.

Questions were included concerning five factors that were chosen as the most reliable and most important of those known to influence the prevalence rate of cervical carcinoma: age,

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† Department of Pathology and the Cytology Service, Memorial Hospital for Cancer and Allied Diseases, and the Division of Pathology, Sloan-Kettering Institute.
‡ Biomathematics Division, Graduate School of Medical Sciences, Cornell University and Sloan-Kettering Institute, and IBM Thomas J. Watson Research Center.
§ Planned Parenthood of New York City, Inc.
Requests for reprints should be sent to Dr. Melamed, Memorial Hospital, 444 East 68th Street, New York, N.Y. 10021.

ethnic origin, age at first pregnancy (as a reflection of early sexual experience), number of children born alive (as a reflection of the number of pregnancies), and net weekly family income (as a reflection of socio-economic status) (Lombard and Potter, 1950 ; Wynder *et al.*, 1954 ; Jones *et al.*, 1958 ; Haenszel and Hillhouse, 1959 ; Terris and Oalmann, 1960 ; Rotkin, 1962 ; Rotkin and King, 1962 ; Boyd and Doll, 1964 ; Christopherson and Parker, 1965). It was felt that answers to direct questions about sexual experience, particularly age at first coitus, frequency of coitus, and number of different sexual partners would not be reliable, and that in this population the number of marital partners for each woman could not be estimated by the number of legal divorces and marriages. In order not to discourage unmarried women from attending Planned Parenthood centres, a direct question about marital status was not included. Indirectly this was obtained during the course of the interview by requesting the husband's first name. Twenty per cent. of the women coming to the centres failed to supply the husband's first name and these at least were thought to be unmarried. This was considered as a possible sixth factor, but most of these women were young and, after correcting for age, there was no association between choice of contraceptive or the prevalence of cervical carcinoma in situ and failure to supply a husband's first name.

Information regarding circumcision status of their marital partners, available only in interviews with the women, was considered to be too unreliable to be used.

At the initial interview the various forms of contraception were described to the applicant, who then made the choice of method. Unless there was medical contraindication, the chosen method was prescribed. The oral steroids prescribed at all centres were of the combination type and in the manufacturer's recommended dosage. A deliberate effort was made to fairly represent all of the commercially available products among those prescribed.

Detailed records of the contraceptives prescribed and used are maintained as a continuing part of the chart for each woman at the centre she attends. Our tabulation of contraceptive use in each case was taken from these records ; thus the data always reflect known minimum periods of time during which the contraceptives were used. For this study we were unwilling to accept information about contraceptive use previous to attendance at one of the centres of Planned Parenthood, and so disregarded it. Thus the new patient was always coded as a contraceptive user of zero time length, according to the method she chose, even though this might be a continuation of the same method she said she had been using before coming to the Planned Parenthood centre.

Recording of Data

Each day the clinical data collected were transferred to IBM key-punch cards. After cytological examinations were complete the diagnoses were added. The data were then transferred from cards to a 1316 disc file on the IBM 360/40 computer at the Computation Center of Cornell University Medical College and Sloan-Kettering Institute. The individual cytological reports were printed on prepared forms by the computer at rates of up to 600 lines per minute, thus making it easily possible to return a separate report for each woman.

Follow-up of Cytological Abnormalities

When cytological evidence or suspicion of carcinoma was found cervical biopsies were recommended. The woman was recalled and re-examined by one of the several gynaecologists working with Planned Parenthood and specifically concerned with this study. Another cytological specimen was obtained, followed by Schiller's iodine test. Biopsy specimens of any suspicious or non-staining areas were taken or, if the cervix appeared normal, specimens were taken of several different representative sites. All biopsy specimens were processed in the department of pathology of Memorial Hospital, and the histological diagnoses were those of two of us (M. R. M. and L. G. K.).

Treatment.—Women who required further treatment were referred to a physician of their choice or to one of the hospitals of the City of New York. For those who wished it, hospital care has also been made available in the gynaecological ward service at Lenox Hill Hospital.[1] Surgical procedures carried out at this latter hospital have been under the direct supervision of one of us (H. D.), and a report on the surgical techniques, complications, and results in over 200 cases is now in preparation. All pathological specimens from surgery performed on the women at Lenox Hill Hospital were examined by two of us (M. R. M. and L. G. K.), and pathological material from surgery performed elsewhere has been obtained for our review. Final histological diagnoses and the type of surgery performed were recorded on punched cards and added to the patient's data file on the disc.

Criteria for Selection of Determinant Cases

In order to achieve prevalence rates as nearly accurate as possible the following criteria were established.

Total Population

All women who had been examined at least once in one of the centres of Planned Parenthood and had had a technically satisfactory cytological specimen taken and submitted for our examination, with complete clinical data, were included in the study. Fewer than 25 cases from over 40,000 originally entered were excluded because of incomplete information ; 450 were excluded because the initial cytological specimen was unsatisfactory and the women failed to return.

Of the remaining 39,954 women, 27,508 selected oral steroids for contraception and 6,809 selected the diaphragm. This analysis is concerned with the 34,317 women in these two groups. For reasons explained above, the intrauterine device users could not be included in this prevalence study but will be considered in subsequent incidence studies. There were too few women choosing other methods (condom, foam, etc.) to warrant their inclusion (Dubrow *et al.*, 1969).

Cases with Carcinoma or Carcinoma in situ

For determination of prevalence rates it was important to identify those patients who could be reasonably assumed to have had carcinoma or carcinoma in situ of the cervix at the time they entered the study. We required that they have (*a*) cytological evidence of carcinoma, or suspicion of it, on initial examination or on repeat examinations carried out within eight months ; or (*b*) that in those patients with a significant but non-diagnostic abnormality on initial cytological examination there be definite evidence of the disease on the first repeat cytological specimen.

Cytological specimens reported as unsatisfactory for evaluation were counted as no specimen, and the first satisfactory specimen was regarded as the initial specimen.

The arbitrary eight-month period was selected to include all patients who had repeat cytological examinations for any reason before their routine annual smear. By selecting cases in this manner we were confident that the patients with lesions actually present at the time of first examination, but inadequately represented in the first cytological sample, were included.

Those patients who had cytological evidence of the disease when they entered the study, as defined above, and then had histological diagnoses confirmed by us of carcinoma in situ,

[1] We are indebted to Dr. Hugh Barber, Director of Obstetrics and Gynaecology at Lenox Hill Hospital, for his support.

carcinoma in situ with microfocal invasion, or invasive carcinoma (one case only) were accepted for determination of prevalence rates. There were some patients with abnormal cytological findings who failed to return or refused biopsy examination. As is shown below, the loss from such cases was random, and did not affect statistical evaluation.

Cases of carcinoma in situ that have subsequently appeared in patients without initial cytological evidence of the disease, as defined above, are not considered in this report. Cases with lesser degrees of epithelial abnormality are also not included, but are being followed, and will be the subject of subsequent communications.

Our criteria for the cytological diagnoses and for the histological diagnoses of carcinoma, carcinoma in situ, and related lesions, based on a long prospective study of this disease, have been described in detail and amply illustrated in previous publications (Koss *et al.*, 1963 ; Koss, 1968). We are aware that some of the lesions we diagnose as carcinoma in situ may be named " precancerous metaplasia," " anaplasia," " dysplasia," " atypical hyperplasia," " significant epithelial abnormality," " cervical intraepithelial neoplasia," and a variety of other terms by some other pathologists. Any of these lesions may be precursors of invasive cervical carcinoma, and though there is controversy about which particular patient with which particular lesion will develop invasive cervical carcinoma, and when—something we cannot predict—there is evidence that invasive carcinoma can be prevented if all women with these precursor lesions are treated (Marshall, 1965).

All cytological and histological examinations were performed without referral to clinical data collected for statistical evaluation and without knowledge of the contraceptive used or contemplated.

Methods of Data Analysis

The initial data analysis compares prevalence rates of carcinoma in situ (including carcinoma in situ with microfocal invasion and the one case of clinically occult invasive carcinoma) in all of the women choosing and using diaphragms with those choosing and using oral steroids, according to documented minimum duration of use.

Then, for women using these contraceptive methods for at least one year, prevalence rates are compared according to each of the five factors that were selected because of their known influence on the rate of the disease. As previously noted, these are age, ethnic origin, age at first pregnancy, number of children born alive, and net family income.

Finally, in order to eliminate bias which might be introduced by the known association between these five factors and the method of contraceptive chosen (Dubrow *et al.*, 1969), three separate random matching programmes have been carried out. Each compares groups of women who have been using their contraceptive method at least one year, and who are matched in regard to all five factors listed above.

In order to carry out these last matching programmes, each woman was provided with a five-digit vector that represented her classification according to each of the five factors. Age at the time of the first cytological examination was indicated by the first digit and divided into five groupings: 20 years or less, 21 to 25 years, 26 to 30 years, 31 to 35 years, and 36 years or older. The second digit indicated which of four ethnic groupings was applicable: White, Negro, Puerto Rican (or Spanish-speaking), or other (mostly Oriental or Indian, and accounting for only about 1·5% of the population). Relatively few Jewish women attended centres of Planned Parenthood, and they have not been separately identified. The third digit referred to age at first pregnancy and included three categories: never pregnant, first pregnant at age 19 or earlier, and first pregnant at age 20 or later. The fourth digit referred to number of live births and comprised two categories: zero to two, and three or more. The fifth digit referred to net weekly family income and consisted of two categories: less than $75/week, and $75/week or more. About half the population attending Planned Parenthood centres report a net weekly family income of less than $75.

Every woman who had been using a diaphragm or contraceptive steroids for at least one year was identified by her five-digit vector (200 such vectors being possible, rather than 240, since women who were never pregnant would necessarily fall into the zero to two category for number of live births). A random computer search was then made for one, two, or three steroid users with identical vectors to each of the diaphragm users, without regard to the cytological or pathological reports on these women. The reason for using three different match ratios is discussed later. This process produced a large number of pairs, triplets, or quadruplets, a small percentage of which were positive—that is, contained cases of carcinoma or carcinoma in situ. If it is assumed that the prevalence of the disease had no association with method of contraception, then the positive members of these positive pairs, triplets, or quadruplets would be roughly one-half, one-third, or one-fourth diaphragm users. Deviations from these ratios may be used to test for a significant association between method of contraception and the prevalence of carcinoma and carcinoma in situ.

Results

Of the nearly 40,000 women who have been seen in the 11 centres of Planned Parenthood since this study began (Dubrow *et al.*, 1969), 27,508 chose to use oral steroids for contraception and 6,809 chose the diaphragm. During the first year after their initial visit there was a relatively large drop-out rate, but continued attendance thereafter was fairly good. Within the population choosing either the diaphragm or steroids were one case of clinically occult invasive epidermoid carcinoma (stage 1A), 14 cases of carcinoma in situ with microfocal invasion, and 192 cases of carcinoma in situ.

The raw data for all women choosing either the diaphragm or steroids are compared in Table I, according to the known minimal length of time each method was used.

TABLE I.—*Uncorrected Prevalence Rates of Cervical Carcinoma in situ for All Women Using the Diaphragm or Contraceptive Oral Steroids, According to Known Minimal Periods of Use*

	Known Minimal Period of Contraceptive Use (Years)					
	0 *	1+	2+	3+	4+	5+
Diaphragm:						
No. of cases Ca. in situ	26	16	16	13	12	11
Total No. of cases	6,809	3,874	3,519	3,178	2,830	2,533
Raw prevalence rates per 1,000	3·8	4·1	4·5	4·0	4·2	4·3
Oral steroids:						
No. of cases Ca. in situ	181	62	36	18	5	2
Total No. of cases	27,508	6,331	3,814	1,931	596	147
Raw prevalence rates per 1,000	6·6	9·8	9·4	9·3	8·4	14†

* Total, including women who had just chosen this contraceptive method at their first visit. The number of women in each column using either contraceptive for a given minimal period of time is cumulative in that it includes all women in subsequent columns known to have longer minimal periods of use.

† It is necessary to point out that this figure is based on only two cases with carcinoma in situ.

The higher prevalence rates of carcinoma in situ[2] among steroid users is not explained by a difference in age between them and the women using diaphragms ; in fact, the women using steroids are generally younger than those using the diaphragm (Dubrow *et al.*, 1969). Age-specific prevalence rates are given in Table II, and compared for the populations

[2] Hereafter, the term " carcinoma in situ " is used in the text and tables in a technically inaccurate sense, for the sake of convenience, to include the few cases of carcinoma in situ with microfocal invasion and the one case of clinically occult invasive carcinoma.

of women who are known to have been using their respective contraceptives for a minimum of at least one year previous to the initial cytological examination. Similar comparisons can be drawn between the women using diaphragms and those who use oral steroids, according to ethnic origin (Table III), age at first pregnancy (Table IV), number of children (Tables IV and V), and net family income (Table VI). In all, there is consistently a higher prevalence rate of carcinoma in situ among the women who chose and used oral steroids for contraception compared with those who chose and used the diaphragm.

TABLE II.—*Prevalence Rates for Cervical Carcinoma in situ Compared According to Age in Women Known to be Using the Diaphragm or Contraceptive Oral Steroids for One Year or Longer*

	Age (Years)					Total
	≤20	21–25	26–30	31–35	36+	
Diaphragm:						
No. of cases Ca. in situ ..	0	2	2	6	6	16
Total No. of cases ..	29	341	653	787	2,064	3,874
Prevalence rates per 1,000	—	5·9	3·1	7·6	2·9	4·1
		4·0				
Oral steroids:						
No. of cases Ca. in situ	0	13	21	24	4	62
Total No. of cases ..	183	1,914	2,227	1,301	706	6,331
Prevalence rates per 1,000	—	6·8	9·4	18	5·7	9·8

TABLE III.—*Prevalence Rates for Cervical Carcinoma in situ Compared According to Ethnic Origin in Women Known to be Using the Diaphragm or Contraceptive Oral Steroids for One Year or Longer*

	Ethnic Origin		
	White	Negro	Puerto Rican/Spanish
Diaphragm:			
No. of cases Ca. in situ ..	1	12	3
Total No. of cases	1,305	2,053	487
Prevalence rates per 1,000 ..	0·9	5·8	6·2
Oral steroids:			
No. of cases Ca. in situ ..	4	46	12
Total No. of cases	724	3,884	1,666
Prevalence rates per 1,000 ..	5·5	12	7·2

It is obviously desirable to correct simultaneously for as many of the known factors influencing the prevalence of this disease as is possible, particularly because these factors are themselves interrelated in varying ways. This was done by the method of vector assignments to each patient, as already described, randomly matching individual patients with identical vectors by computer. As in the previous tables, the women who are matched have all been using their respective contraceptive methods for a minimum of one year. Again, it must be emphasized that the prevalence rates of carcinoma in situ are determined by the number of women with the disease who

TABLE IV.—*Prevalence Rates for Cervical Carcinoma in situ Compared According to Age at First Pregnancy and Number of Live Births in Women Known to be Using the Diaphragm or Contraceptive Oral Steroids for One Year or Longer*

	Never Pregnant	Age at First Pregnancy			
		≤19 years		20 years+	
Diaphragm:					
No. of cases Ca. in situ ..	0	7		9	
Total No. of cases	208	1,106		2,560	
Prevalence rates per 1,000 ..	—	6·3		3·5	
		No. of Live Births			
		0–2	3+	0–2	3+
No. of cases Ca. in situ ..		3	4	3	6
Total No. of cases		357	749	1,365	1,195
Prevalence rates per 1,000 ..		8·4	5·3	2·2	5·0
		Age at First Pregnancy			
		≤19 Years		20 Years+	
Oral steroids:					
No. of cases Ca. in situ ..	1	29		32	
Total No. of cases	414	2,991		2,926	
Prevalence rates per 1,000 ..	2·4	9·7		11	
		No. of Live Births			
		0–2	3+	0–2	3+
No. of cases Ca. in situ ..		6	23	16	16
Total No. of cases		1,033	1,958	1,595	1,331
Prevalence rates per 1,000 ..		5·8	12·0	10·0	12·0

TABLE V.—*Prevalence Rates for Cervical Carcinoma in situ Compared According to Number of Live Births in Women Known to be Using the Diaphragm or Contraceptive Oral Steroids for One Year or Longer*

	No. of Live Births	
	0–2	3+
Diaphragm:		
No. of cases Ca. in situ	6	10
Total No. of cases	1,722	1,944
Prevalence rates per 1,000	3·5	5·1
Oral steroids:		
No. of cases Ca. in situ	22	39
Total No. of cases	2,628	3,289
Prevalence rates per 1,000	8·4	12·0

TABLE VI.—*Prevalence Rates for Cervical Carcinoma in situ Compared According to Economic Status in Women Known to be Using the Diaphragm or Contraceptive Oral Steroids for One Year or Longer*

	Family Net Income	
	< $75/Week	≥ $75/Week
Diaphragm:		
No. of cases Ca. in situ	11	5
Total No. of cases	1,441	2,433
Prevalence rates per 1,000 ..	7·6	2·1
Oral steroids:		
No. of cases Ca. in situ	34	28
Total No. of cases	3,310	3,021
Prevalence rates per 1,000	10	9·3

TABLE VII.—*Result of Simultaneous Multifactor* Random Matching of Women Using the Diaphragm and Women Using Contraceptive Oral Steroids Longer than One Year*

Match Ratio Diaphragm/Steroid User	No. Women Successfully Matched	No. of Pairs	No. of Pos. Pairs†	Diaphragm Pos. Pairs/Steroid Pos. Pairs‡		
				Expected	Observed	Critical Values for 5% Significance Level
1:1	4,702	2,351	35	17:18 or 18:17	12:23	12:23, 23:12
				Diaph. Pos. Triplets/Steroid Pos. Triplets‡		
		No. of Triplets	No. of Pos. Triplets†	Expected	Observed	Critical Values for 5% Significance Level
1:2	5.493	1,831	52	17:35 or 18:34	9:43	11:41, 24:28
				Diaphragm Pos. Quads/Steroid Pos. Quads‡		
		No. of Quads	No. of Pos. Quads†	Expected	Observed	Critical Values for 5% Significance Level
1:3	5,884	1,471	58	14:44 or 15:43	8:50	9:49, 21:37

* Age, ethnic group, age at first pregnancy, number of live births, and economic status were all matched simultaneously.
† Positive pairs, triplets, or quadruplets refers to a matched group of women that includes one with carcinoma in situ. In two separate instances, two women with carcinoma in situ fell into one quadruplet; in both cases the two women were steroid users and each quadruplet was counted as one.
‡ Diaphragm positive pairs, triplets, or quadruplets refers to matched groups in which the patient with carcinoma in situ was using a diaphragm; steroid positive pairs, triplets or quadruplets refers to matched groups in which the patient with carcinoma in situ used steroids.

had cytological evidence of it on entering the study, and subsequent histological confirmation by cervical biopsy or conization. The results of these matched comparisons are indicated in Table VII, for ratios of diaphragm users to steroid users of 1:1, 1:2, and 1:3.

The three different ratios were investigated because the number of women from each group that can be matched varies according to the ratio. The overall number of women using steroids longer than one year is nearly twice the number using a diaphragm for a similar minimum period, hence the 1:2 ratio seems most reasonable. The diaphragm users, however, tend to be older than the women using steroids (Dubrow *et al.*, 1969), and many of the older women using diaphragms and younger women using steroids cannot be matched at a 1:2 ratio. Matching at the additional ratio of 1:1 included more of the older women using diaphragms ; and matching at a ratio of 1:3 included more of the younger women using steroids (Table VIII). At all ratios a consistently higher prevalence rate for cervical carcinoma in situ was found among the steroid users (Table VII).

TABLE VIII.—*Variation in Age of Matched Populations of Diaphragm Users and Steroid Users According to the Match Ratio (See Table VII)*

Match Ratio Diaphragm/ Steroid User	No. of Women in Each Age Group Successfully Matched					
	Age (Years)					
	≤20	21–25	26–30	31–35	36+	Total
1 : 1	48	682	1,270	1,358*	1,344	4,702
1 : 2	63	1,008	1,779*	1,632	1,011	5,493
1 : 3	64	1,280	2,068*	1,608	864	5,884

* Median age.

We also examined the matched populations to determine whether the difference in prevalence rates could be explained by a systematically greater failure to obtain recommended biopsy specimens from the diaphragm users. The number of cases in each group that should have had biopsy examinations but did not is indicated in Table IX. Biopsy failures were completely random and do not explain the difference in observed prevalence rates between diaphragm users and steroid users.

TABLE IX.—*Comparison of Number of Women in Each Successfully Matched Group Who Had Cytological Suspicion of Cervical Carcinoma But in Whom Recommended Biopsy Specimens Could Not be Obtained*

Match Ratio. Diaphragm User/Steroid User	No. of Women with Biopsy Specimens Not Obtained. Diaphragm User/Steroid User
1 : 1	5 : 6
1 : 2	4 : 7
1 : 3	2 : 6

Discussion and Conclusions

A study of the prevalence rates of uterine cervical carcinoma in situ among women attending centres of the Planned Parenthood of New York City is reported.

There is a small but significant difference between the population choosing and using the diaphragm and the population choosing and using oral steroids for contraception. It can be attributed either to a decreased prevalence rate for women using a diaphragm or to an increased rate for women using oral steroids. The difference is consistently present in subsets corrected for each of five factors known to influence the prevalence rate of cervical carcinoma: age, ethnic origin, age at first pregnancy (as a reflection of early sexual experience), number of live births, and family income (as a reflection of socio-economic status). When corrections for all five factors are carried out simultaneously there is still a significantly higher prevalence rate for cervical carcinoma in situ within the population choosing and using steroid contraceptives.

The reason for the difference in prevalence rates is not clear. One could postulate some still unknown factor(s) in the make-up, behaviour, or habits of a woman that would alter her probability of developing cervical carcinoma and at the same time impel her to choose a particular contraceptive.

In several different studies a lower rate of cervical carcinoma was found for women who had used barrier contraceptives (diaphragm or condom), compared with women using no contraceptive (Terris and Oalmann, 1960 ; Boyd and Doll, 1964 ; Aitken-Swan and Baird, 1965). Though not confirmed by all investigators (Lombard and Potter, 1950 ; Wynder *et al.*, 1954 ; Jones *et al.*, 1958 ; Rotkin and King, 1962), this finding, if true, could well account for the differences we found. Experimental animal studies can be cited to show that human smegma is carcinogenic in susceptible mice (Pratt-Thomas *et al.*, 1956), thus providing a rationale for the concept that barrier contraceptives such as the diaphragm and condom are protective. Also, there is an increased rate of cervical carcinoma in prostitutes (Røjel, 1953), an increased frequency of coitus among women who develop cervical carcinoma (Terris and Oalmann, 1960 ; Boyd and Doll, 1964), an increased probability of carcinoma in women who first experience coitus at an early age (Rotkin, 1962), and virtually no cervical carcinoma in nuns (Gagnon, 1950).

On the other hand, the cervicovaginal epithelium is a known target organ for steroids, and it is considerably altered by oestrogens and progestogens (Taylor *et al.*, 1967 ; Koss, 1968). There is experimental evidence that prolonged administration of large doses of oestrogens can cause uterine cervical carcinoma in mice (Allen and Gardner, 1941). The constancy of prevalence rates in Table I does not suggest that we are seeing this kind of direct hormonal effect, but it must be remembered that the data in Table I are not corrected for any of the known factors that affect prevalence rates of this disease. Table I must not be interpreted as giving incidence rate information, since it results from initial examinations only (as is true of all data in this report), and there is a presumed loss of some cases due to diagnosis and treatment elsewhere. The opportunity for loss of this kind increases with increasing time in attendance at the centre previous to the initiation of this study, and would be expected to mask any trend in Table I.

A study of the incidence rates of uterine cervical carcinoma in matched populations of women using various contraceptives is now in progress and should help to clarify some of the questions raised. First, it is essential that the differences noted in prevalence rates be confirmed by incidence rates before we can be entirely sure that these differences are not artifactitious. Data from the population of women who are wearing an intrauterine device will be particularly useful, since there is neither a barrier effect nor a hormonal effect with this particular contraceptive.

Clearly, the long-term well-being of many women is involved in these questions, and the health of women attending centres of Planned Parenthood of New York City has been of primary concern to us. During the course of this study every effort has been made to find and treat the women with cervical carcinoma or carcinoma in situ and related epithelial abnormalities while the lesions are still early enough to be cured in 100% of the cases. All women attending centres of Planned Parenthood are assured of prompt and proper treatment, regardless of choice of contraceptive. Preliminary data from centres of Planned Parenthood, unrelated to this report, show a sharp drop in the number of cases of invasive carcinoma of the cervix after establishing the policy of searching out and treating all women with carcinoma in situ. It is our conviction that death and disability from cancer of the cervix in any population can be greatly reduced, regardless of the method of contraception used, if a programme of routine yearly cytological examinations is established and all cases of carcinoma in situ are treated. So long as regular visits to a physician are mandatory for women who are using the steroid contraceptives in order to obtain a prescription there is a possibility for them to have better

medical care, with less danger from cancer of the cervix, than any other group of women.

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Dr. Christopher Tietze critically reviewed much of the data with us and contributed many helpful suggestions.

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Results of Treatment of Thyrotoxicosis after Postoperative Relapse

D. G. McLARTY,* M.B., CH.B. ; W. D. ALEXANDER,† M.D., F.R.C.P.ED. ; R. McG. HARDEN,‡ M.R.C.P.GLASG.
D. H. CLARK,§ M.D., CH.M., F.R.C.S.

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Summary: Ninety patients who had a recurrence of thyrotoxicosis after thyroidectomy have been reviewed. All 10 patients who had a second operation and 18 out of 20 patients treated with a full course of antithyroid drugs relapsed. These results differ greatly from the results of treatment of the first episode of thyrotoxicosis, whether by thyroidectomy or antithyroid drugs. Radioiodine is the treatment of choice in this group of patients, despite the high incidence of hypothyroidism.

Introduction

Most follow-up studies of patients treated by thyroidectomy make reference to the incidence of recurrence of thyrotoxicosis after operation. The prognosis for such relapsed patients with reference to subsequent morbidity and to the effectiveness of subsequent treatment is, however, uncertain. This study describes the results of treatment in 90 patients who relapsed after thyroidectomy. In this situation the results of treatment by drugs and surgery are very different from those of treatment of the first episode.

Methods

Ninety patients (77 (85·6%) female and 13 (14·4%) male) who had been treated by thyroidectomy for thyrotoxicosis and who had subsequently relapsed were reviewed. The age distribution of the patients at the time of operation is shown in Table I. Sixty-one (68%) of the thyroidectomies had been performed in the Western Infirmary, Glasgow, and 29 (32%) in other hospitals. Thirty-three (36·7%) of the operations were performed before 1950, 43 (47·8%) during 1951–60, and 14 (15·5%) during 1961–6.

TABLE I.—*Age and Sex Distribution of 90 Patients who Relapsed after Thyroidectomy*

	Age in Years					
	-20	21–30	31–40	41–50	51–60	61–70
Male	0	3	8	1	1	0
Female ..	4	16	31	20	5	1

The time of relapse of thyrotoxicosis following the initial operation is shown in Fig. 1. Twelve (13·3%) patients remained euthyroid for more than 15 years before relapse of thyrotoxicosis occurred

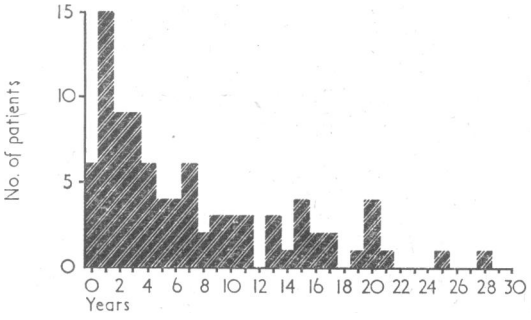

FIG. 1.—Time of relapse after thyroidectomy.

* Hall Fellow in Medicine.
† Reader in Medicine.
‡ Lecturer in Medicine.
§ Consultant Surgeon.
Gardiner Institute, Western Infirmary, Glasgow W.1.