CERVICO-VAGINAL CYTOLOGY EVALUATION IN WOMEN RECEIVING NORETHISTERONE OENANTHATE INJECTIONS FOR CONTRACEPTION

By

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Introduction

The last decade has witnessed a spurt in interest in contraceptive technology owing to the alarming increase in world population. A major breakthrough was achieved in this field with the introduction of oestrogen-progestogen pills which are very effective contraceptive agents if taken regularly, but which have had poor acceptance in developing countries like ours because the motivation required for daily pill taking is lacking. Consequently efforts are underway to test long acting hormone preparations given either by injections or in the form of implants. Encouraged by the preliminary results is a WHO initiated trial with 200 mg. injections of Norethisterone Oenanthate, the Indian Council of Medical Research (I.C.M.R.) in March 1981 initiated a Multicentric clinical trial with this preparation at its 16 Human Reproduction Research Centres in different parts of the country in the Obstetrics and Gynaecology departments of Medical College of Allahabad, Alleppey, Baroda, Bikaner, Jammu and Lucknow, Institute for Research in Reproduction and K.E.M. Hospital at Bombay, Vivekanand Institute of Medical Sciences and R. G. Kar Medical College at Calcutta, Kasturba Hospital, New Delhi, K.E.M. Hospital, Pune and Kilpauk Medical College Hospital, Govt. Lying-in-Hospital, Govt. Kasturba Hospital and Institute of Obstetrics and Gynaecology at Madras.

A Cytology Evaluation Unit has been provided by ICMR at the K.G. Medical College, Lucknow since March 1981. The function of this unit is to monitor by cytological evaluation the oncogenic potential of the different contraceptive preparations investigated at the various ICMR HRRCs listed above. For the present trial, all participating centres were directed to collect cervical smears before starting the injections and at one yearly intervals thereafter and to send them to Lucknow for cytologic evaluation. Though a total of 2353 women were enrolled for the study, pretreatment smears were not collected in 404, and in these only posttreatment smears have been examined. Out of 1949 women in whom pretreatment smears had been examined, only 897 returned for follow up while the rest dropped out of the study and this paper deals with the cytological findings in these 897 women and also in the 404 in whom only posttreatment smears have been evaluated.

Materials and Methods

The injectable contraceptive used in this study was an oily suspension of 200 mg. of Norethisterone Oenanthate in one C.C. of Benzyl Benzoate and Castor Oil in a Ratio

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of 6:4, manufactured by Schering A.G. Berlin, administered intramuscularly. After the initial injection at the time of introduction in the study, all subjects were given a second injection 2 months later. Thereafter, the subjects were divided into two groups-one receiving the injections two monthly and the other three monthly. All centres were instructed to take scrape smears at the time of enrolment and at yearly intervals thereafter from two sites—(a) from squamocolumnar junction of cervix and (b) from endocervical canal. The smears were to be fixed in Absolute Alcohol and sent to Lucknow where they were stained according to the Papanicolaou technique and graded into Negative, Inflammation, Dysplasia (mild, moderate and severe), Carcinoma-in-situ and Frank carcinoma according to WHO classification of 1973.

Observations and Results

Pretreatment cytology

Cytologic examination of pretreatment smears in 1949 women revealed 'normal' smears in 1546 (81-8%), 'inflammatory' smears in 365 (18.1%) and dysplasia in 21 (1.07%) while 17 smears (0.9%) were unsuitable for evaluation. Eighteen of the dysplastic smears were mild and 3 were moderate. As stated earlier, only 897 women returned for follow up and this included only 11 of the 21 women with pretreatment dysplastic smears and regression of the lesion to normal was seen in all 6-12 months later without any treatment.

Follow-up Cytology

A total of 2148 posttreatment smears had been examined in 1301 women for periods ranging from 6 to 48 months of hormone use. The fate of the 11 pretreatment dysplastic smears that could be followed has already been commented upon but during the study period, 23 fresh cases of mild dysplasia were encountered. The incidence of dysplasia in the follow-up smears was thus 1.7% which is higher than 1.07% incidence observed in the pretreatment group. Pretreatment smears were available in 15 of 23 post treatment dysplasia cases and the reports had been 'normal' in 9 and 'inflammation' in 6. The period of follow-up when dysplasia was detected varied from 6 to 30 months. In 14 cases, the change was detected on first follow-up 6-12 months after starting the injections. In 5 cases, the dysplasia was detected on the second follow-up, in 2 cases on the third follow-up and in 2 on the fourth follow-up. The intervening reports in these 9 cases had been either 'normal' (6 cases) or 'inflammation' (3 cases).

None of the 23 patients with posttreatment dysplastic smears were asked to discontinue the injections as the dysplasia in all cases was only of mild degree, but inspite of this, 9 women dropped out of the study on their own. The remaining 14 cases who continued with the injections were re-examined 6-12 months later and the dysplasia had regressed to normal in all without any treatment.

Detailed analysis of posttreatment smears in relation to period of Norethisterone Oenanthate use is given in Table I from which it is evident that though the incidence of inflammatory smears remained lower than the pretreatment figure of 22.8% at all stages of contraception, the incidence of trichomonal infection showed a steady rise from the pretreatment figure of 0.3% to 8.2% at 48 months but trichomonal infection was a precursor of dysplasia in only one case.

On the whole, the incidence of dysplasia, showed a flactuating trend with in-

TABLE I
Incidence of Inflammatory and Dysplastic Smears in Relation to Period of Hormone Use in 1301 Women

	Pretreatment incidence	Follow up in months							
		6	12	18	24	30	36	42	48
No. of women examined	897	625	826	91	392	97	73	32	12
No. and incidence of inflammatory smears	206 (22.8%)	92 (14.5%)	115 (13.6%)	15 (11.1%)	52 (13.2%)	15 (15.8%)	11 (15.1%)	4 (12.5%)	2 (8.2%)
No. and incidence of trichomonal infection	3 (0.3%)	2 (0.3%)	5 (0.5%)	1 (1.08%)	2 (0.5%)	2 (2.1%)	2 (2.7%)	2 (6.2%)	1 (8.2%)
No. and incidence of dysplastic smears	11 (1.3%)	9 (1.4%)	8 (0.9%)	2 (2.2%)	2 (0.5%)	2 (2.1%)	—	—	—

creasing duration of hormone use, rising from the pretreatment figure of 1.3% to 2.2% at 18 months, and then declining to 0.5% at 24 months and again rising to 2.1% at 30 months. Interestingly, no dysplastic smears were detected in 67 women who had taken the injections for 3 years or more.

Further an attempt has been made to analyse relationship, if any, between the incidence of dysplasia and factors such as age, parity and previous use of contraceptives with regards to both the 21 pretreatment dysplasia cases and the 23 dysplasias detected on follow-up in 1301 women and a definite relationship appears to exist with incidence of dysplasia and increasing age and parity (Tables II and III). In the same age and parity groups, however, the incidence of dysplasia was higher after hormone use than in non-users. It seems wiser, therefore, not to advocate this mode of contraception to women older than 35 years and with parities of 3 and above most of whom will have completed their families whose interests will be better served by resorting to a permanent method of conception control such as sterilization. As regards previous use of contraceptives, the incidence of dysplasia was found higher on follow-up in the previous contraceptive users particularly in previous hormonal contraceptive users (Table IV). Constant cytologic follow-up studies are, therefore, advocated for this group to pick up recurrant or progresive cases of dysplasia.

Discussion

Till recently it was the Oestrogen component of hormonal contraceptives which was chiefly implicated in the development of cervical carcinogenesis. With introduction of long acting progestogen contraceptives it has become essential to test the

TABLE II

Relationship Between Age and Pattern of dysplasia in Pretreatment Smears in 1949 Women and Follow up Smears in 1301 Women

Age group	Pretreatment smears		Follow up smears	
	No. of cases	No. and percentage showing dysplasia	No. of cases	No. and percentage showing dysplasia
Upto 20 years	175	2 (1.1%)	23	1 (4.3%)
21-25 years	957	8 (0.8%)	492	10 (2.03%)
26-30 years	695	9 (1.4%)	565	6 (1.06%)
31-35 years	118	2 (1.7%)	196	5 (2.4%)
36-40 years	4	Nil	25	1 (4.0%)
Total	1949	21	1301	23

TABLE III

Relationship Between Parity and Incidence of Dysplasia in Pretreatment Smears of 1949 Women and Follow up Smears of 1301 Women

Parity	Pretreatment smears		Follow up Smears	
	No. of cases	No. and percentage showing dysplasia	No. of cases	No. and percentage showing dysplasia
1	262	Nil	187	2 (1.1%)
2	703	5 (0.9%)	445	6 (1.3%)
3	512	10 (1.9%)	342	14 (4.1%)
4 and above	471	6 (1.2%)	327	1 (0.3%)
Total	1949	21	1301	23

TABLE IV

Relationship Between Previous Use of Contraceptives and Incidence of Dysplasia in Pretreatment smears (1949 Women) and Follow up Smears (1301 Cases)

Type of contraceptive previously used	Pretreatment smears			Follow up smears		
	No. of cases	No. and percentage showing dysplasia		No. of cases	No. and percentage showing dysplasia	
IUD	229	1 (0.9%)	1/469 (0.2%)	145	5 (3.1%)	8/290 (2.7%)
Hormone	63	Nil		48	2 (4.1%)	
Condoms	175	Nil		97	1 (1.1%)	
None	1482	20 (1.3%)		1011	15 (2.4%)	
Total	1949	21		1301 1	23	

oncogenic potential of these compounds too, on longterm use. Since there is no report on this aspect in the available literature and as we had a sizable group of subjects receiving Norethisterone Oenanthate injections, we thought it worthwhile to institute cytological studies in these women. In the present study, 1301 women receiving Norethisterone Oenanthate injections for period ranging from 6 to 48 months

have been followed-up. No case of dysplasia was seen to progress to a higher grade or to frank malignancy during the period of follow-up. On the contrary, follow-up available in 11 of the 21 dysplasias detected in pretreatment smears and 14 of the 23 dysplasias encountered on follow-up showed spontaneous regression of the lesion to normal 6-12 months later. In an earlier study in 35 women conducted at this centre with the same dose of Norethisterone Oenanthate, only 1 case of mild dysplasia was encountered on follow-up and this, too, regressed to normal spontaneously 6 months after its detection (Engineer *et al* 1980).

The accumulated cytologic follow-up data in this study suggests that Norethisterone Oenanthate injections can be used with impunity for periods upto 48 months for family spacing. Longterm study of the women in the present series is mandatory and is being continued both in users and those who have discontinued the injections to determine oncogenic culpability of the longterm use of this hormone.

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