

Abnormal cervical cytologic, colposcopic and histologic findings in exposed DES young Israeli Jewish women

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Summary: A consistently higher rate of abnormal cervical cytology, colposcopic and histologic findings in 89 DES exposed Israeli Jewish women was found as compared to 318 women in a control group. This trend however reached statistical significance for abnormal colposcopic and histologic findings only in the 25-34 age group. The higher rate of abnormal findings can be attributed to DES exposure and not to an excess of other risk factors in the study group. Routine cytologic and colposcopic examination is recommended for DES exposed Israeli Jewish women who are otherwise at low risk for development of cervical neoplasia.

INTRODUCTION

The possible association between intrauterine diethylstilbestrol (DES) exposure and cervical intraepithelial neoplasia (CIN) was for some time controversial⁽¹⁻⁹⁾. In 1984, however, the DESAD project, in a large study, found that the rate of CIN in DES exposed daughters was twice as high as in a matched comparison group of unexposed women⁽¹⁰⁾. It has been suggested that this is due to a greater susceptibility to carcinogen of the large transformation zone of DES exposed women^(2, 10). The exact cause is however still not clear⁽¹¹⁾.

Jewish women are at low risk for cervical neoplasia⁽¹²⁾. The purpose of the present study was to evaluate whether the reported association between intrauterine

DES exposure and CIN was true for Israeli Jewish women as well.

MATERIAL AND METHODS

The study group comprised 89 Israeli Jewish women examined in our cervical cytology and colposcopy clinic during the 7 years between 1979 and 1986. The mothers of 35 of these women confirmed the intake of DES during pregnancy while the mothers of the remaining 54 women remembered taking progesterone or unspecified hormones during pregnancy. Cervical or uterine anatomical anomalies typical of intrauterine DES exposure were observed in 79 (88.8%) of the study group women. The control group consisted of 318 women examined in the same clinic during the same period who were in the same age range as the women in the study group. None of them had anatomical anomalies attributable to intrauterine DES exposure.

Women of both groups underwent cervical cytologic and colposcopic examination. Cervical biopsy for histologic examination was taken if an atypical transformation zone was seen colposcopically. The analysis relates to cytologic, colposcopic and histologic findings during the initial clinic visit. Statistical analysis was done using chi square and Mantel-Haenszel relative

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Table 1. - Characteristics of the study group (DES exposed) and control group women.

	Study group		Comparison group		p (**)
	No.	%	No.	%	
Total (*)	89	100.0	318	100.0	
<i>Age (years)</i>					
24	60	67.4	102	32.0	<0.0001
25-34	28	31.4	202	63.5	
35	1	1.1	11	3.4	
<i>Marital status</i>					
Single	31	34.8	79	24.8	N.S.
Married	57	64.0	230	72.3	
<i>Descent</i>					
Asia-Africa	8	8.9	119	37.4	<0.0001
Europe-Israel	81	91.0	197	61.9	
<i>Education</i>					
Elementary	0	0.0	26	8.1	0.01
Higher education	87	97.7	290	91.1	
<i>Sexual activity</i>					
Active	87	97.7	313	98.4	N.S.
Not-active	2	2.3	5	1.5	
<i>Age at first coitus</i>					
<18	25	28.1	80	25.1	N.S.
>19	56	62.9	230	72.3	
<i>Presenting symptom</i>					
Routine examination	30	33.7	74	23.2	
Post-coital bleeding	4	4.5	73	22.9	<0.0001
Irregular bleeding	3	3.4	31	9.7	
Infertility	21	23.6	13	4.0	
Other	24	26.9	102	32.1	
<i>Parity</i>					
Nullipara	65	73.0	129	40.6	<0.0001
Parous	24	27.0	189	59.4	
<i>Menstrual cycle</i>					
Regular	16	18.0	287	90.3	0.05
Irregular	73	82.0	31	9.7	

(*) Some characteristics were not known in all women.

(**) N.S. = Not significant.

risk with Miettinen's test based confidence limits.

The characteristics of the women in the study and control group are presented in Table 1. In the control group there was a significantly higher proportion of women aged over 25, of women of Asian-African descent, of women with only elementary education and of women whose presenting symptoms were post-coital or irregular bleeding. In the study group there was a statistically higher proportion of women with irregular menses, of women whose presenting symptom was infertility and of nulliparous women. With regard to other characteristics, such as marital status and age at first coitus, there was not statistical difference between the two groups. A similarly high proportion of women in both groups was sexually active (97.7% and 98.4% respectively).

Of 52 patients in the study group who tried to conceive, 29 (55.8%) were infertile, while among 229 women in the control group only 21 (9.2%) were infertile. This differences was statistically significant (p<0.05).

RESULTS

Table 2 presents the rate of abnormal cytologic, colposcopic and histologic findings according to age group in the study and control group. In the age group 24 or under there was a higher rate of abnormal cytologic and colposcopic findings in the study group, but the differences were statistically not significant. The rate of abnormal histologic findings was similar in this age group. In the 25-34 age group there was a significantly higher rate of abnormal colposcopic and histologic findings in the study group. In this group the relative risk of any abnormal finding in the study group was 2.1 (1.3-3.3; p<0.01).

The rate of abnormal cytologic findings in the 25-34 age group was also higher in the study group than in the control group, however the differences was not statistically significant.

Among the 89 women in the study group, 37 (41.6%) underwent cervical biopsy and histologic examination showed CIN in 6 (6.7%) (CIN 1 in 4, CIN 2 in one and CIN 3 in one). Among the 318 women in the control group, 72 (22.6%)

Table 2. – The rate of abnormal cytologic, colposcopic and histologic findings in the study and control group women according to age group¹.

	Age group					
	<24			25-34		
	Total (100%)	Abnormal findings No.	%	Total (100%)	Abnormal findings No.	%
<i>Cytology</i>						
Study group	60	5	8.3	28	3	10.7
Control group	120	3	2.9	202	13	6.4
Relative risk	2.2 (0.7-7.7) ²			1.3 (0.4-4.6) ²		
<i>Colposcopy</i>						
Study group	60	22	36.7	28	15	53.6
Comparison group	102	29	28.4	202	43	21.3
Relative risk	1.4 (0.8-2.2) ²			2.0 (1.1-3.7) ³		
<i>Histology</i>						
Study group	60	2	3.3	28	4	14.3
Control group	102	4	3.7	202	9	4.4
Relative risk	0.9 (0.2-3.5) ²			3.2 (1.3-8.2) ³		
<i>At least one abnormal test</i>						
Study group	60	24	40.0	28	15	53.6
Control group	102	31	30.0	202	52	26.0
Relative risk	1.3 (0.8-2.1) ²			2.1 (1.3-3.3) ⁴		

¹ Relative risks are followed by 95% confidence limits in brackets

² Not significant

³ 0.0 < p < 0.02

⁴ p < 0.01.

underwent cervical biopsy and CIN was found in 13 (4.1%) (CIN 1 in 6, CIN 2 in 2 and CIN 3 in 5).

The relative risk of having any abnormal finding remained significantly higher in the study group than in the control group also after accounting for age at first coitus 1.6 (1.2 - 2.4; p < 0.01).

No statistical analysis was done for the age group older than 35, since there was only one such patient in the study group.

DISCUSSION

Our results indicate a consistently higher rate of abnormal cervical cytologic, colposcopic and histologic findings in DES exposed Israeli Jewish women than in a control group in the same age range examined in the same period and in the same clinic. This trend, however, reached statistical significance for abnormal colposcopic and histologic findings only in the 25-34 age group, perhaps due to the small number of women with abnormal findings in the younger age group.

Invasive carcinoma was not detected in any of the women of both groups.

The difference in abnormal findings between the two groups was not due to an excess of commonly accepted epidemiologic risk factors in the study group, such as sexual activity, early initiation of coitus, high parity or low socio-economic status. The rate of sexually active women was similarly high in both groups, and among the DES exposed women there was not a higher proportion of women who started sexual intercourse at an early age. A higher rate of abnormal findings in the study group was found also when the age at first coitus was accounted for. Asian-African descent and lower education, indirect indicators of low socio-economic status in Israel, were less common in the study group. The rate of nulliparity was higher in the study group.

It can be argued that not all study group women were actually DES exposed, since it was confirmed in only 39.3% of them. However, the remaining women had typical cervical and uterine anatomical anomalies considered also by others⁽¹³⁾ to be adequate evidence for intrauterine DES exposure. In addition a high rate of menstrual cycle disturbances and infertility,

typical among DES exposed women^(14, 15), was also observed in our study group.

It is not clear whether the rate of abnormal cytologic, colposcopic and histologic findings in our study group represents the rate among all DES exposed Israeli women, since most of the women in our study group had anatomical anomalies and it is therefore selective. Orr *et al.*⁽⁵⁾ reported no correlation between the presence of cervical anomalies in DES exposed women and abnormal epithelial findings. The rate of women without anatomical anomalies in our study group is too small to clarify this issue.

Our control group was also highly selective since a large proportion of the women were referred to the clinic for symptoms which may be related to cervical neoplasia. In spite of this bias, the rate of abnormal findings was significantly higher in the study group.

Although no data were available with regard to other risk factors such as the number of sexual partners and the rate of genital papilloma virus infection, our data seem to indicate that the higher rate of abnormal cervical findings including CIN can be attributed to intrauterine DES exposure. The largest rate of abnormal findings was on colposcopic examination (40.8%). This is in line with other reports of DES exposed women^(2, 7). The reported CIN rate in DES exposed women ranges from 0.4% to 26.6%^(5, 7). Our rate of 6.7% is within this range.

Thus, intrauterine DES exposure represents a risk factor which justifies routine cytologic and colposcopic examination in Israeli Jewish women who are otherwise at low risk for the development of cervical neoplasia.

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