

Exposure of girls to oestrogens during fetal development

Report of a survey of maternal records

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SUMMARY. In a two-partner practice with 5,000 patients where oestrogens had never been prescribed during pregnancy, it was found on examining the records, that at least eight girls had been exposed to oestrogens in utero, two of them to stilboestrol. Three of them have since been examined with negative results. In a quarter of cases no information was available from the records.

Introduction

Studies in the United States of America (Ulfelder, 1973) have shown a correlation between vaginal carcinoma near puberty and exposure to stilboestrol in utero. Some cases of this previously extremely rare condition have occurred in girls in this age group in several countries in what has appeared to be almost an epidemic. It was found that in 85 per cent of cases stilboestrol had been given to their mothers during the first five months of pregnancy. Not only is this an unpleasant and dangerous condition sometimes remaining silent until at an advanced stage, but screening involves vaginal examination and hospital attendance or admission at a sensitive age, with a risk of serious psychological consequences.

Stilboestrol is the only hormone to have been implicated so far (Ulfelder, 1974) but other steroid oestrogens which have been available for a shorter time may on further investigation also be shown to have had a harmful effect. About 30 per cent (some reports give a considerably higher figure, of female fetuses exposed to stilboestrol in utero have developmental abnormalities of the vagina and cervix and of these, less than 0.1 per cent are estimated to go on to produce malignant changes.

I tried to quantify the risk in a practice in South-west England and to indicate possible further lines of enquiry. Until more is known about the effects of other oestrogens I assumed that they should also be regarded as suspect. Accordingly, information was sought about the prescribing of any oestrogenic hormones in pregnancy.

Method

A list of girls born in the years 1953–1965 inclusive was compiled through the practice age-sex register and from this a list of mothers. Where available the mothers' National Health Service records were searched for any possible reference to the prescription of oestrogen during pregnancy, but the patients were not consulted.

It was known that neither partner had at any time prescribed oestrogens in pregnancy, but it was thought possible that with movement of the population some may have moved into the area having been exposed to hormones elsewhere.

When the notes referred to a hospital, I wrote asking for more information.

Results

On comparing the age-sex structure of the practice with the figures from the 1971 Census in England and Wales it was found that the number of girls in these age groups did not differ appreciably from the national norm. The rate of turnover in the practice of 7.7 per cent a year for 1972 and 1973 was low. This was deduced from the number of records withdrawn by the executive council, the practice size remaining constant at 5,000 shared between two principals.

The medical records of 416 girls aged between eight and 20 years were examined. In 42 cases the mother's notes were unobtainable because the girl was living away from home, the mother had died, was separated, or was registered with another doctor. As expected this problem was greater with the older girls and it was not considered worthwhile trying to inspect records of girls born before 1953. In a further 59 cases the records did not contain enough information about whether drugs had been prescribed. In some cases pregnancies passed unnoticed (the period under study occurring before registering with this practice). It was possible to be reasonably certain that 307 of the 315 girls whose records were thought to be reliable had not been exposed to oestrogens.

In eight cases there was clear reference to the prescription of oestrogens, but no indication of the duration of treatment except a recommendation in one. There were two sets of twins and one pair were exposed to stilboestrol. Four cases were exposed to ethinyl oestradiol and two to 'TACE.'

TABLE 1
OESTROGENS PRESCRIBED WHILE 416 FEMALE FETUSES WERE IN UTERO

Year	No oestrogen	oestrogen	No record		Total
			No notes	Inadequate notes	
1953	9	0	9	2	20
1954	11	0	9	2	22
1955	24	1	4	6	35
1956	27	0	2	10	39
1957	19	2	2	6	29
1958	24	2	0	8	34
1959	23	1	2	10	36
1960	24	1	5	3	33
1961	22	0	1	5	28
1962	36	0	1	2	39
1963	25	0	2	1	28
1964	31	1	4	2	38
1965	32	0	1	2	35
<i>Total</i>	307	8	42	59	416

Case 1

Given ethinyl oestradiol 0.05 mg b.d. for threatened miscarriage at 12 weeks.

Cases 2 and 3

Given stilboestrol 5 mg at 6-7 weeks pregnancy. No indication is recorded, but the mother believes this was to suppress lactation in view of the further pregnancy. Binovular twins screened with negative findings at examination under anaesthetic.

Cases 4 and 5

The previous two pregnancies had miscarried. A hospital letter: "She has been given a supply of 'Amenerone forte' which she will continue until late pregnancy." It appears that treatment may have started before a period had been missed. Binovular twins. ('Amenerone forte' = Ethisterone 50 mg with ethinyl oestradiol 0.05 mg).

Case 6

Given 'TACE' at 14 weeks; no indication is recorded.

Case 7

Given TACE at eight weeks as the previous pregnancy had miscarried. Screened by examination under anaesthetic at her parents' request with negative results.

Case 8

Given 'Mixogen' at six weeks pregnancy for "white discharge" ("Mixogen" = Ethinyl oestradiol 0.0044 mg with methyltestosterone 3.6 mg).

Discussion

It appears that in a practice with a stable list of 5,000 patients, low turnover and where oestrogens have never been prescribed in pregnancy, that at least eight young girls had been exposed to oestrogens in utero, two of them to stilboestrol. Details were obtainable from only threequarters of the cases. In a little less than half of the remainder there were no records to examine. In the remainder the records were so sketchy that it was impossible to tell what had been prescribed. In no case was it possible to determine precisely the dose and duration of treatment. An at risk group has been identified with much toil and without reference to the patients, whose memories were not thought to be reliable enough. A patient enquiry would also have provided considerably more work and generated unnecessary anxiety.

In the five cases where reference was found to hospital treatment during the pregnancy an enquiry was made to the hospital. No information was available in any case as the hospital records had been destroyed. It is suggested that the policy of destroying obstetric records with other records after a period of time should be reviewed because of the long latent period and the possibility of other problems coming to light if further associations are proved in future years. These figures suggest that records of pregnancies between 1955 and 1960 are the most likely to yield results in a survey of this kind in England, although cases of carcinoma after exposure to stilboestrol occurred in USA from 1945 with a peak about five years later.

There is certainly a fairly urgent need to obtain figures from other practices, in particular those where the use of stilboestrol or other oestrogens can be recalled, in order to form an estimate of the size of the population at risk. It is believed that the figure in USA may be as high as 16,000 for stilboestrol alone. Once identified the need to screen carefully those girls exposed to stilboestrol would appear to be compelling in spite of the difficulties and risk of emotional trauma.

Acknowledgement

I am most grateful to Mr Douglas Bamford for his advice and encouragement in pursuing this enquiry and for examining my patients.

I would also like to thank Miss Christine Carter for her invaluable help in the preparation of the list of mothers, Mrs Dorothy Hawkins for her patient assistance in compiling the report, and the anxious mother who first stimulated my interest in the subject after she had seen a television programme (Brasher, 1973) and realised that her own daughter was at risk.

REFERENCES

- Brasher, C. (1973). *Danger—Take Two a Day*, BBC TV, 26 October.
Ulfelder, H. (1973). *American Journal of Obstetrics and Gynecology*, 117, 794–800.
Ulfelder, H. (1974). Personal Communication.
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