

PREGNANCY FOLLOWING CERVICAL CARCINOMA *IN SITU*

A Review of 60 Cases

BY

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AMONG 503 patients with cervical carcinoma *in situ* treated at the National Women's Hospital in the years 1950-65 the modal age and parity were 33 years and 2 respectively, showing that many women with this disease are of relatively low parity and of reproductive age. Treatment of the disease by hysterectomy seems, if a lesser procedure is safe, unduly drastic management of a large number of women still in the prime of their reproductive careers. Conservative treatment by conization or amputation of the cervix was considered by the *Lancet* (Editorial Comment, 1964) as "reserved for younger women and those very anxious to preserve their fertility". Although this type of treatment for cervical carcinoma *in situ* was reported on as long ago as 1952 by Carter *et al.* there are as yet few reports on fertility and pregnancy following it. Boyd *et al.* (1963) reported 23 pregnancies, of which 16 came to term, in 56 women under the age of 35 treated for carcinoma *in situ*. Fettig and Kuhn (1963), in a review of 1,208 cervical conizations from the literature (the number performed for carcinoma *in situ* was not stated), found a conception rate of 23.4 per cent and an abortion rate of 23.5 per cent which was said to correspond with that "from large abortion statistics". Bylina (1964) reported 502 cases of carcinoma *in situ* treated by electroconization; 103 patients subsequently became pregnant but details were not given. Green (1966b) reported 15 pregnancies occurring after 200 consecutive conizations performed in the investigation of positive cervical smears between April 1963 and June 1965, 11 being in patients with carcinoma *in situ*.*

In this paper a series of 60 pregnancies occurring in 50 patients previously treated in the years

1957-65 for carcinoma *in situ* will be reported and a conception rate will be estimated from the total number of conservatively-treated patients in whom pregnancy might have been expected to occur subsequently. The effect of treatment in producing abortion, premature labour, and cervical dystocia will be examined and the significance of the lesion discussed.

MATERIAL

From January 1950 to December 1965, 503 cases of cervical carcinoma *in situ*, of which 33 (6.6 per cent) were in nulliparae, have been diagnosed and treated at the National Women's Hospital. Since 1956 a conservative approach to diagnosis and treatment has been favoured so that, up to December 1965, 317 patients have been treated by local excision of the lesion and 186 by hysterectomy (Table I). Up to June 1966 no patient was lost to follow-up.

Although 32 of the conservatively-treated group have had positive follow-up smears at periods ranging from six months up to nine years there has been no case of true progression to invasive cancer.

TABLE I
Treatment and Subsequent Pregnancies
503 Cases of Cervical Carcinoma in situ

Treatment	All Cases	Subsequent Pregnancies
Punch biopsy	4	2
Ring (<2 cm. deep) biopsy	70	17
Cone (>2 cm. deep) biopsy	231	30
Amputation of cervix ..	12	1
Hysterectomy	186	—
Total	503	50

* These 11 are included in the present report.

One 70-year-old woman had minimal carcinoma *in situ* diagnosed in a ring biopsy of the cervix performed at the same time as a radical vulvectomy for a florid vulval cancer; two years later (1965) invasive cancer of the cervix was found alongside a local recurrence of the vulval lesion. One case in 503 approaches the expected incidence of invasive cervical cancer in any group of women of this size.

Because of doubts as to the significance of carcinoma *in situ* in the natural history of invasive cervical cancer (Green, 1966a) four patients seen in 1965 have had no further treatment since the clinical, colposcopic, and punch-biopsy diagnosis of the lesion. Two have since become pregnant and one has been delivered at term; subsequent colposcopy with punch-biopsy in this latter case has shown only cervical dysplasia.

Age and parity of the 50 patients with subsequent pregnancies. The youngest patient at the time of diagnosis of cervical carcinoma *in situ* was 16 years old; since a cone biopsy in 1960 she has had two normal term deliveries. Twenty-one patients were 20–29 years old, 27 were 30–39 years old, and one was 41 years old. Table II shows the parities of the 50 patients prior to treatment of the cervical lesion.

RESULTS

Of the 50 patients 42 have subsequently conceived once, 6 twice, and 2 three times. Four of the 50 were pregnant at the time of cone biopsy, but these four pregnancies are not included in the total of 60. The 60 pregnancies resulted in 38 living children, one neonatal death after term delivery, two neonatal deaths from prematurity, one ectopic pregnancy, one unwitting termination of pregnancy, and 12 first trimester abortions (Table III). Six patients are undelivered, one being at present in the first trimester, 3 in the second and 2 in the third.

Effect of Cervical Treatment on Fertility

(a) *Infertility factors already present.* Of the 317 patients not treated by hysterectomy 200 were under 41 years old when the carcinoma *in situ* was diagnosed, the oldest patient subsequently conceiving being 41 years old. The case histories of these 200 patients were reviewed for any

TABLE II
Parity of Patients Prior to Treatment
50 Cases

Previous parity	0	1	2	3	4	5	6	7	8
No. of patients	3	2	13	7	9	6	7	2	1

TABLE III
Results in 60 Pregnancies

	No.	Infants	
		Born	Surviving
Abortion 14	—	—
Premature labour 6	7	5
Term labour 34	34	33
Undelivered 6	—	—
Totals 60	41	38

TABLE IV
Infertility Factors in 200 Patients Under 41 Years Old

Infertility Factor	No. of Cases
Sterilization at or before treatment 10
Intrauterine contraceptive device used since treatment 7
Husband sterilized 1
History of infertility investigation or adoption of children 16
Five or more years infertility at time of diagnosis 43
Premature menopause (age 35) one year after treatment 1
Widowed, divorced, or separated 6
Total 84

factors (other than the treatment of cervical carcinoma *in situ*) that might have precluded subsequent pregnancy. As a result the number of patients in whom pregnancy might have been expected was reduced to 116 (Table IV).

The numbers of patients with a definite history of infertility (59 or 11.3 per cent) and of nulliparae (33 or 6.6 per cent) in the total series appear high at first glance and might seem to indicate that cervical carcinoma *in situ* tends to occur in women of less than average fertility. However, of 533 consecutive cases of *invasive* cervical cancer treated at the National Women's

TABLE V

Interval Between Treatment and Subsequent Pregnancy

Interval (months)	1	2	3	4-12	13-24	25-48	49-72
No. of patients	1	5	1	19	14	8	2

Hospital in the years 1958-65, 58 or 10.1 per cent were nulliparous. Also the average parity of the 503 *in situ* cases was 3.1, as compared to 3.4 for the invasive cancers and 2.8 for the 56,356 women aged 16 to 50 years having viable births in New Zealand in 1964 (N.Z. Government Statistician, 1965).

(b) *Interval between treatment of cervix and conception.* The average time between the treatment of the carcinoma *in situ* and the last menstrual period prior to the (first) subsequent pregnancy in the 50 patients was 16 months. The range is shown in Table V.

Thus, from (a) and (b) above, 50 (43.1 per cent) of 116 patients under 41 years old with no known infertility factor who were treated conservatively for carcinoma *in situ* subsequently conceived, four-fifths of them doing so within two years. This finding does not appear to show any major adverse effect on fertility.

Effect on Pregnancy

(a) *First trimester abortion.* Fourteen of the 60 pregnancies ended in the first three months, one being the second ectopic pregnancy in an otherwise infertile woman. The case of a three weeks pregnancy discovered in the excised uterus of a patient in whom cervical carcinoma *in situ* had been diagnosed by ring biopsy eight weeks previously is also included in this group. Three patients had normal deliveries at term after the cervical treatment and before having their abortion; one of these three patients had another delivery at term later. Since it is unlikely that these three abortions can be ascribed to the cervical biopsy there remain nine abortions which were possibly caused by either conization (7 patients) or ring biopsy (1 patient). The abortion rate attributable to the cervical treatment, 9 in 49 completed pregnancies or 18.4 per cent, is similar to that of 23.5 per cent quoted by Fettig and Kuhn (1963), and that of 21.7 per cent found by Boyd *et al.* (1963). It seems to

confirm the opinions of these authors that cervical conization is not followed by an untoward incidence of abortion. Nevertheless, since two of the abortions occurred in a woman who had previously had six normal pregnancies it is likely that conization can alter cervical function in some patients so that there is a predisposition to abortion.

(b) *Premature labour.* Six patients with this complication gave birth to seven infants weighing less than 2,500 g., five of whom survived. Those dying of prematurity were a 28 weeks foetus weighing 680 g. and a 32 weeks foetus of 700 g. whose twin (1,160 g.) survived. Excluding the twin pregnancy (which was also complicated by placenta praevia) the incidence of premature labour was 5 in 53 (9.4 per cent), or a little higher than the overall rate of 8.9 per cent for 4,651 deliveries in the hospital in 1965.

(c) *Complications in term pregnancies.* The one perinatal death in 34 term pregnancies occurred in a country hospital and it was not possible to establish a satisfactory cause of death: the same mother has twice since been delivered of living infants at term. Two patients were delivered by Caesarean section, one electively because of a previous Manchester repair (which had revealed unsuspected carcinoma *in situ* in the amputated cervix) and the other for prolonged (76 hours) labour due to cervical dystocia. In another patient, during vaginal examination after 6 hours of strong labour, a hard, apparently-unyielding cervix was felt to give way suddenly; delivery quickly followed and an extensive cervical tear required suturing. The same pattern was seen in another patient after 23 hours in labour although with less damage to the cervix. The last three cases, all of whom had had conization of the cervix for carcinoma *in situ*, demonstrate clearly that cervical fibrosis with subsequent dystocia may result from this type of treatment.

Of the remaining 30 term pregnancies one was abnormal in that labour lasted only 27 minutes;

TABLE VI

Duration of Labour in 34 Deliveries at Term

Hours	.. ½	2-12	12-24	28	76	Un-known
No. of patients	1	20	7	1	1	4

TABLE VII
Positive Smears During Follow-up

Years of Follow-up	No. of Patients	No. with Positive Smears	Year of Follow-up when Smear Positive
9	..	2	1
8	..	2	1
7	..	2	1
6	..	2	-
5	..	10	2
4	..	5	1
3	..	3	-
2	..	12	1
1	..	9	1
<1	..	3	2
Totals	..	50	10

it is possible that a weakened or incompetent cervix was responsible for this precipitate course. The average duration of labour at term in 30 patients for whom the information was available was approximately 11 hours (Table VI). Only one of these was a nullipara (17 hours in labour); the other two nulliparae had an early miscarriage and a second ectopic pregnancy respectively.

Follow-up Cytology

Table VII shows the length of follow-up of the 50 patients up to 30th June, 1966, the number with positive cervical smears during that time, and the time of follow-up at which these were positive.

Thus one fifth of the patients in the pregnancy series had positive smears at some time or other during their follow-up period. The corresponding figures for the total series were 62 (18.1 per cent) of 343 originally treated conservatively and 8 (5.0 per cent) of 160 originally treated by hysterectomy. An additional 26 hysterectomies, 22 ring or cone biopsies, and 7 vaginal vault biopsies which have been performed have not eliminated all positive follow-up smears and there currently remains a total of 35 patients with positive follow-up smears, 32 after conservative treatment and 3 following hysterectomy. Our present policy is to do nothing further to these patients other than to make a regular clinical and

colposcopic examination and to review the original or subsequent histology for any possible invasion. The history of one patient is worth recording in detail:

She was a very intelligent para-5 Maori aged 35 who had a positive cervical smear in January 1960. Cone biopsy showed "micro-invasive carcinoma *in situ*". She refused hysterectomy after four follow-up smears in the first year were all positive. At two years, when they were still positive, a further cone biopsy showed the same histological appearances. Pregnancy then ensued and she was delivered normally at term. Two positive smears in the next nine months preceded another normal pregnancy and delivery. A ring biopsy at four years showed the same lesion and at five years, when her smears were still positive, she agreed to hysterectomy only because she wanted no further children. The excised cervix, although very fibrosed, appeared otherwise normal, but histological sections still showed a focus of "microinvasive" carcinoma *in situ*. During the whole five years the cervix always appeared normal.

Such cases as this, quite apart from indirect statistical evidence, seem to cast some doubt on the actual significance of carcinoma *in situ* in the natural history of true invasive cervical cancer (Green, 1966a). Certainly subsequent pregnancy does not appear to accelerate the progression to invasion of *in situ* cancer even when it appears to have been excised incompletely.

DISCUSSION

Although the results in these pregnancies following treatment of cervical carcinoma *in situ* are not unfavourable as regards the proportion of abortions, premature labours, and complications in term deliveries, there is little doubt that cone biopsy does influence subsequent pregnancy. Of the nine abortions possibly related to the cervical biopsy procedure eight occurred in patients on whom conization had been performed. Also five of the six premature labours and all three term labours with cervical dystocia were in patients after cone biopsy. Thus 16 of the 30 patients on whom conization was performed had these complications of pregnancy as compared to only two of the 17 ring biopsy cases. If future

child-bearing is important in a patient to be treated conservatively for carcinoma *in situ* it would seem preferable to perform a ring rather than a cone biopsy.

The present series of 60 pregnancies in 50 patients is intended not only to show the effects of cervical operative procedures on subsequent pregnancy but also to demonstrate that if carcinoma *in situ* is handled conservatively substantially normal pregnancies may follow—with no apparent increased risk of the patients' developing subsequent invasive cancer, even with some positive smears in the follow-up period. The fact that normal child-bearing is possible after carcinoma *in situ* has been diagnosed is important to the large number of women of relatively young age and low parity with this cervical lesion. The results obtained also suggest that cone biopsy is adequate, and hysterectomy unnecessarily radical, treatment for cervical carcinoma *in situ*.

The fact that a disease which is claimed by so many authors to be a precursor of invasive cervical cancer can be treated effectively and safely by local excision and can be followed by pregnancy without evidence of progression of the disease should raise some doubts as to the significance of the lesion. The failure of the diagnosis and treatment of large numbers of *in situ* cancers (after more than a decade of cytological screening in some centres) to accelerate the *already-present* decline in the incidence of invasive cervical cancer to eliminate invasive cancer from cytologically-screened population groups, or to alter mortality rates (McKinnon, 1963; Green, 1966a), must reinforce these doubts. Although Bryans *et al.* (1964) regarded it as unnecessary to wait for proof based on mortality statistics before accepting the value of cytology, a reduction in the death rate must surely be the final arbiter of its value. Such a reduction has not yet been observed in British Columbia after 15 years of cytological screening (Green, 1966a).

The proportion of cases of cervical carcinoma *in situ* which progress to invasion and the average time elapsing before the invasive stage is reached are two factors upon which the biological significance of the disease obviously depends. In recent literature there has been a tendency to decrease estimates of the proportion developing

invasion, the range varying from 100 per cent in 1952 (McKelvey, 1952) to 10 per cent in 1962 (Graham *et al.*, 1962). At the same time the estimated length of the pre-invasive phase seems to have been prolonged. Ten years has been mentioned frequently whereas the highest of the three estimates of Boyes *et al.* (1962) was 20 or more years. This tendency to prolong estimates of the length of the pre-invasive phase and decrease those of the proportion of cases developing invasion implies that the significance of cervical carcinoma *in situ* may not be so great as has previously been thought. Consequently the possibility of eliminating invasive cancer by mass cytology campaigns must be regarded as being extremely doubtful.

SUMMARY

A series of 60 pregnancies following the conservative treatment of 50 patients with cervical carcinoma *in situ* is presented. These 50 patients comprise 43·1 per cent of the number who might have been expected to become pregnant out of a total of 503 patients treated in the years 1950–65. Of the latter 317 (68·2 per cent) had, up to December 1965, been treated by local excision. Ten of the patients who became pregnant and 32 of the total of 317 patients treated conservatively have had positive follow-up smears at intervals of up to nine years. From the 60 pregnancies there resulted 13 abortions, one unwitting termination, 6 premature labours, and 34 term deliveries. The number of surviving infants was 36 and 6 patients have not yet been delivered.

Whilst the number of patients with abortion, premature labour, or cervical dystocia was not greatly increased it is considered that cervical conization tends to cause these complications and should be replaced by a ring-type biopsy when future child-bearing is important. It is considered that both the series of patients who became pregnant and the total series demonstrate that local excision is adequate treatment for cervical carcinoma *in situ*. The significance of this lesion as a precursor of invasive cancer is discussed and it is concluded that the risk of this and the value of mass cytology screening campaigns in the elimination of invasive cancer are not so great as appears to be thought at present.

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