PAPERS AND SHORT REPORTS

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Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours

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Abstract

To examine the possibility that cytotoxic drugs may cause sterility or congenital malformations in the offspring of women of childbearing age who are cured of cancer a study was conducted of the obstetric histories of 445 long term survivors treated in this unit with chemotherapy for gestational trophoblastic tumours between 1958 and 1978. After completing treatment 97% of those who wished for a pregnancy (49% of all women studied) conceived and 86% had at least one live birth. All these women had received methotrexate. Of the 47 women who wished to conceive and whose combination therapy included cyclophosphamide, 37 (79%) had a live birth. Women who received three or more drugs were less likely to have a live birth than those who received methotrexate alone or with only one other drug ($p < 0.001$). There was no statistically significant excess of congenital malformations.

These results are strong evidence that the cytotoxic drug regimens used in this unit for treating gestational trophoblastic tumours are compatible with the preservation of fertility in most women and not associated with any increase in congenital abnormalities.

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Introduction

An increasing number of women of childbearing age are becoming long term survivors after treatment with cytotoxic chemotherapy. Although these agents are well recognised as a potential cause of sterility,[1] there are some drug regimens that do not cause permanent impairment of fertility in women. This is apparent in those who have been treated for gestational trophoblastic tumours, some of whom have subsequently conceived.[2-4] Even if fertility is unimpaired, there is still the danger that the cytotoxic chemotherapy may have a mutagenic effect on the ova.[5] Hence it is important to record any birth defects in the progeny of patients treated with these drugs. Since 1958 this unit has treated over 800 women with choriocarcinoma or invasive mole. With the aim of identifying cytotoxic drug regimens that were compatible with fertility and not teratogenic, we studied the subsequent obstetric histories of those women who entered remission after receiving chemotherapy for a gestational trophoblastic tumour.

Patients and methods

Between 1958 and the end of 1978, 590 women were treated with cytotoxic chemotherapy for choriocarcinoma or invasive mole. Of these patients, 99 died from their tumour or from complications of treatment. Thirty four patients who were not resident in Britain could not be traced. Questionnaires sent in July 1980 to the remaining 457 survivors were returned by all but 17. For five of these up to date medical and obstetric details were available from hospital records. From questions about health and hospital admissions since completing treatment we were able to determine the incidence of second malignancies.[6] We present here the data on the outcome of pregnancies and the development of any children born since completing treatment. Results were tested for significance using a χ^2 or Fisher's exact test (two sided), as appropriate.

Drug regimens had altered considerably since 1958. Hence rather than describe particular drug regimens, we report the total amount of each cytotoxic drug received and the total duration of treatment. All regimens entailed intermittent administration of cytotoxic agents in courses of two to 10 days' duration with drug free periods between courses lasting five to 15 days in almost all instances. Folinic acid was routinely given after methotrexate from 1963 onwards. There was no long term daily drug administration, and maintenance treat-

ment was not given in any instance. The methods by which treatment was tailored to risk factors and the drug protocols used are described elsewhere.[7 8]

Results

Up to date obstetric records were available on 445 women. Of the 217 women who wished to conceive, 187 (86%) succeeded in having at least one live birth, 23 (11%) conceived but did not achieve a live birth, and seven (3%) who wished to conceive failed to do so. In addition, six women conceived despite not wanting a pregnancy and had a termination, and one woman was still pregnant at the completion of the study. These seven women are excluded from the analysis. Since a live birth was the desired outcome for the women who wished for a pregnancy, it is of interest to compare the characteristics of the women who succeeded in having at least one live birth with those of the women who conceived and had no live births and with those of the women who wished to conceive but failed. Data on the 221 women who did not try for and did not have a pregnancy are presented where appropriate but comment is confined mainly to the three groups of women who wished to conceive.

The mean duration of chemotherapy was four months. The average age on completion of treatment was 24·9 years for those who had a live birth, 24·4 years for those who conceived but had no live birth, and 24·4 years for those who did not conceive at all. The average age of the women who did not wish for a pregnancy was 31·5 years.

A total of 125 women were over 30 at the completion of treatment. All 23 of these who wanted to conceive did so, and 19 (83%) had one or more live births. There was no statistically significant difference between the number of women in this age group who did not have a live birth and the number among women under 30. Similarly there was no difference between the two age groups in the number of drugs received. The mean time interval from completion of treatment to first pregnancy was 2·7 years and to the first live birth 3·2 years. The mean time interval from completion of treatment to the date of last contact was 7·7 years for those with a live birth, 6·6 years for those who conceived but had no live birth, and 4·4 years for those who did not conceive at all.

For each of the four groups of women table I shows the mean and maximum amounts of cytotoxic drug received. Methotrexate was given to all but two patients, neither of whom had tried to conceive. Analysis of each drug individually showed no statistically significant difference between the mean amounts given to the women who achieved a live birth and those who did not. Live births occurred after all of the agents used apart from cisplatin and VP 16-213 (etoposide). There was little difference in the maximum doses given between the group who had a live birth and the groups who did not.

Combination chemotherapy was given to 43% of women who had a live birth, 57% of those who conceived but did not have a live birth, and 71% of those who failed to conceive. These differences, however, were not statistically significant. Nevertheless, there was a difference when considering the number of drugs received. Those women who were given three or more drugs in combination were less likely to have a live birth or to conceive at all when compared with those women given methotrexate alone or in combination with only one other drug (χ^2 for trend 11·68; $p<0·001$) (table II). We could not identify whether particular regimens were associated with this occurrence, as the numbers receiving any given combination were too small to permit reliable conclusions.

Those who received actinomycin D or vincristine, however, were less likely to have a live birth than the women who did not receive either drug ($p<0·01$ and $p<0·05$ respectively). None of the other drugs used in combination showed this significance and none—including actinomycin D and vincristine—showed any dose response relation. We emphasise, however, that the numbers receiving doxorubicin (Adriamycin), etoposide, melphalan, vinblastine, and cisplatin were small, and so these drugs could not be satisfactorily assessed. Interestingly, there was no difference in the outcome of pregnancy between those who received the alkylating agent cyclophosphamide and those who did not: of the 47 women who received this drug, 37 (79%) had a live birth.

A total of 368 conceptions resulted in 273 (74·2%) live births, eight (2·2%) stillbirths, two neonatal deaths, 53 (14·4%) miscarriages, two ectopic pregnancies, and 30 (8·2%) terminations. Two of the stillbirths were anencephalic, five had a gestation of less than 34 weeks, and a physically normal baby was stillborn after rupture of the uterus. Both neonatal deaths were in children born after a gestation of 32 weeks. Applying the yearly national perinatal mortality rates[9] to the number of live births and stillbirths occurring in each corresponding year showed that a total of 5·2 perinatal deaths would have been expected. Even so, the observed number (10) was not a significant excess ($p=0·08$).

Although patients were advised that it might be unwise to conceive within one year of completing treatment, 45 women did so. These conceptions resulted in 31 live births, one anencephalic stillbirth, seven miscarriages, and six terminations.

TABLE I—*Mean and maximum doses of cytotoxic drug received by women in each of the four pregnancy groups. (Numbers of women given in parentheses)*

	At least 1 live birth (187)		No live births (23)		Failed to conceive (7)		Not tried to conceive (221)	
	Mean	Max	Mean	Max	Mean	Max	Mean	Max
Methotrexate alone (g)	1·26 (106)	6·0	1·56 (10)	2·6	1·30 (2)	1·6	1·10 (71)	2·0
Methotrexate in combination (g)	1·22 (81)	6·8	1·33 (13)	6·5	1·95 (5)	4·5	2·20 (148)	34·5
Actinomycin D (mg)	8·9 (49)	29·0	8·5 (11)	22·0	9·8 (5)	15·0	11·8 (111)	48·0
Vincristine (mg)	7·4 (37)	17·0	7·1 (8)	22·0	7·3 (4)	18·0	11·3 (83)	46·0
Cyclophosphamide (g)	3·6 (37)	8·0	3·2 (6)	7·0	4·5 (4)	8·0	4·7 (82)	9·0
6-Mercaptopurine (g)	5·9 (33)	30·0	5·3 (3)	14·0	1·3 (3)	2·0	5·4 (56)	30·0
6-Azauridine (g)	150 (29)	300	220 (5)	300			220 (44)	1670
Hydroxyurea (g)	3·6 (14)	8·0	6·3 (3)	16·0	3·0 (3)	6·0	9·4 (49)	47·0
Doxorubicin (mg)	100 (5)	100	150 (2)	200	100 (1)	100	140 (25)	400
Etoposide (mg)							613 (16)	990
Melphalan (mg)	18 (3)	24					33 (12)	84
Vinblastine (mg)	20 (2)	20					37 (9)	80
Cisplatin (mg)							396 (7)	800

TABLE II—*Number of drugs received by women according to pregnancy group*

No of drugs	Women with at least 1 live birth	Women who conceived but had no live birth	Women who failed to conceive	Total
≥3	43 (23%)	10 (43%)	5 (71%)	58
<3	144	13	2	159
Total	187	23	7	217

PROGENY

In addition to the two anencephalic stillbirths, five other cases of congenital abnormality were discovered within seven days of birth; these were (one case each) spina bifida, tetralogy of Fallot, talipes equinovarus, collapsed lung, and umbilical hernia. Applying the yearly rates of congenital abnormality in England and Wales as reported by the Registrar General (1966-72)[10] and the Office of Population Censuses and Surveys (1973-81)[11] showed that 5·8 cases would have been expected. The slight excess of congenital abnormality among children in this study was not significant ($p>0·05$).

Several abnormalities were found later than one week from birth. A boy conceived within two months of his mother completing treatment developed desquamative fibrosing alveolitis within one month of birth but later recovered; however, a sister born three

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years later developed a similar lung disease at 6 months of age and died. A brother born a year later developed normally. The sibling of the child with spina bifida was found to have an asymptomatic heart murmur, and one neonate with tachycardia developed normally after treatment with digoxin. One child was educationally subnormal, and a girl suffered a cot death at four weeks. The 10 mothers of these children showed no significant difference in age, time from completion of treatment to conception, amount of each drug, or number of drugs received when compared with the mothers of children born without any abnormality ($p > 0.05$).

Discussion

These results show that out of 217 women who tried to become pregnant after undergoing chemotherapy for gestational trophoblastic tumour, 187 (86%) succeeded in having at least one live birth and only seven (3%) did not conceive at all.

There was no difference in age at completion of treatment between those who had a live birth and those who did not conceive. In contrast to studies which have shown little ovarian recovery over the age of 30,[12-14] there was no significant difference in the ability to conceive or the outcome of pregnancy in women over 30 compared with those who were younger.

There was a difference in the length of follow up among the three groups who wished to conceive, notably 7·7 years for those with a live birth compared with only 4·4 years for those who did not conceive. It might be postulated, therefore, that with longer follow up some of those women might become pregnant.

Shamberger *et al* showed that high dose methotrexate has little effect on menstruation and pituitary gonadotrophin concentrations.[15] In our study all patients who wished for a pregnancy had received methotrexate, and live births occurred after total doses of up to 6 g. Live births occurred after all the other agents that were given except for cisplatin and etoposide, and for each drug there was no significant difference between the mean and maximum doses given to the women in each of the three groups. Other studies have shown that cyclophosphamide causes a high incidence of ovarian failure.[16,17] Our results disclosed no significant difference in the outcome of pregnancy between those who had received cyclophosphamide and those who had not, and of the women who wanted a pregnancy and had received this drug 79% had a live birth. Those women who had received actinomycin D or vincristine (or both), however, were less likely to have a live birth than those who had not. These findings are difficult to interpret, as unlike cyclophosphamide these drugs have not previously been found to be agents that commonly cause infertility. Women who had received three or more drugs were at a greater risk of not having a live birth. Actinomycin D and vincristine were given to more women in combination than any of the other drugs, and when given in combination they may suppress fertility. Even though vincristine does not appear to cause ovarian failure when given with methotrexate,[15] our study does suggest that the effect of vincristine on fertility should be investigated further, especially when given with drugs such as actinomycin D. It is important to note in our study that total drug doses were not high and that they were given intermittently and in a sequential way. There was no response relation between drug dosage and subsequent fertility.

Results of two previous studies suggested an increase in the number of miscarriages in women treated with chemotherapy for trophoblastic disease.[2,3] In our, far larger study the miscarriage rate (144/1000) was slightly lower than that in the previous studies (156 and 151/1000) and compared favourably with total fetal wastage rates in normal populations (237 and 295/1000).[18,19] Although not statistically significant, there was an increase in perinatal mortality when compared with figures for England and Wales. This is not surprising and probably results from the fact that many women have an abnormal uterus as a consequence of their tumour.

Cytotoxic drugs have been implicated as teratogenic when given during pregnancy[20] but it is uncertain whether they have an effect on later conceptions. Apart from case reports, there have been only a few studies on the progeny of women previously treated for cancer. Among a group of women treated for Hodgkin's disease an excess of abnormal offspring was found in women who had received chemotherapy and radiotherapy.[21] Likewise McKeen *et al* recorded five (13%) malformations in 40 children born to women intensively treated for Hodgkin's disease.[22] Conversely, no birth defects or developmental abnormalities were seen in 24 children whose mothers had received chemotherapy for Hodgkin's disease at Stamford.[13] Li *et al* found no excess of congenital malformations in the progeny of 84 women treated for childhood cancers,[23] and Ross found no excess of malformations in 78 infants born to women treated for trophoblastic diseases.[24] Among the 281 live births and stillbirths in our study there was no statistically significant excess of congenital malformations.

We conclude that the cytotoxic drug regimens used in this unit for treating gestational trophoblastic tumours are compatible with the preservation of fertility in most women and do not appear to be associated with any increase of congenital anomalies in the offspring. This is probably due to the relative safety of methotrexate, since all of the women who wished to conceive had received this drug and 97% of them succeeded in becoming pregnant. Furthermore, when combination chemotherapy was used it was most commonly given in a sequential manner, rather than combining all drugs in the same course. Initial results of studies using sequential combination chemotherapy for Hodgkin's disease suggest that there is less resulting sterility than after the combination of mustine, vincristine, procarbazine, and prednisolone alone.[25]

Although preservation of normal childbearing is of secondary importance to curing patients of cancer, this study shows that both objectives may be achieved. It is important to remember, however, that cytotoxic drugs are potentially mutagenic and teratogenic and that certain regimens may be associated with an increased risk of infertility and congenital abnormality.

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"Third drug" trial: comparative study of antihypertensive agents added to treatment when blood pressure remains uncontrolled by a beta blocker plus thiazide diuretic

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Abstract

Hydralazine, labetalol, methyldopa, minoxidil, prazosin, and placebo were compared when added by random allocation to atenolol 100 mg and bendrofluazide 5 mg daily in a series of 238 hypertensive patients inadequately controlled by the beta blocker-diuretic combination. Atenolol was withdrawn in those allocated to labetalol, and minoxidil was given only to men. The order of acceptability was: placebo, hydralazine, prazosin, methyldopa, minoxidil, labetalol. Minoxidil was more effective than the other active drugs, which had similar potency to one another. All the active agents were more effective than placebo.

Hydralazine was the most generally suitable third drug, with prazosin a close second. Minoxidil was especially effective in patients with less severe hypertension but the same regimen caused fluid retention in those with more severe disease. Labetalol should probably be introduced at a low dose (150 mg daily) even when replacing full doses of a previously administered beta blocker.

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Introduction

There is now much evidence that many of the complications of hypertension may be prevented by adequate control of the blood pressure.[1 2] Recommended initial drug treatment is usually with a beta adrenergic blocking agent or thiazide diuretic.[3] Where reduction of blood pressure is inadequate with a single drug the beta blocker and diuretic may be used together in a two drug regimen[3 4]; some patients, however, may not achieve satisfactory control even with this combination of drugs, so that a third drug may be required.[3 4] Various different agents have been used in this role but there is only limited evidence to indicate which is most suitable.[5]

Among the drugs that may be added to a beta blocker-diuretic combination are methyldopa, hydralazine, prazosin, and minoxidil. Alternatively, labetalol (a combined alpha and beta blocker) may be substituted for a simple beta blocker.[3 4] Each of these drugs has been shown to have an additional hypotensive effect when given in such circumstances—for example, methyldopa,[6 7] hydralazine,[8 9] prazosin,[8 10 11] labetalol,[12 13] minoxidil.[14] We, however, do not know of any controlled prospective study evaluating these "third step" drugs concurrently.

The following trial was therefore undertaken to compare both the efficacy and side effects of five different active drugs used as a third agent in patients whose blood pressure remained inadequately controlled by beta blocker and thiazide diuretic given together.

Patients and methods

Hypertensive patients aged 18-65 years were recruited from three blood pressure clinics in Glasgow (at the Royal Infirmary, Western Infirmary, and Stobhill General Hospital) and from the Royal

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