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Fertility in Patients with Gestational Trophoblastic Tumors treated with Etoposide

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Abstract—*The effect of etoposide containing drug combinations on reproductive performance was studied in women successfully treated for gestational trophoblastic disease between* 1977 *and* 1984. *Of the* 74 *women who wished to get pregnant* 57 (77.0%) *succeeded in having at least one live birth while five* (6.8%) *have ongoing pregnancies. Of eight* (19.8%) *women who have not become pregnant two* (2.7%) *had previous infertility problems antedating the development of gestational trophoblastic disease. The miscarriage rate was* 124/1000. *There was only one case of foetal death and one congenital abnormality (microcephaly possibly associated with cytomegalovirus infection) among* 79 *live births and stillbirths. This study indicates that etoposide (VP16-213) as is currently used in this unit for the treatment of gestational trophoblastic tumour is unlikely to have any long-term efffect on fertility in most women.*

INTRODUCTION

PROGRESS in the management of patients with gestational trophoblastic disease has resulted in an almost uniformly curable disease [1–3]. Since most of these patients are in the reproductive age group, concern about ovarian function and fertility is important. A study of patients treated up to 1978 showed that fertility was maintained in the great majority [4]. However, little is known about the effects of the recently introduced potent antineoplastic drug etoposide, (VP16-213) which is also of value in a wide range of neoplasia [5–7]. Fear of a possible gonadotoxic effect was raised when ovarian dysfunction was observed in patients with gestational trophoblastic disease treated with short intensive courses of this drug [8]. We have therefore studied our patients treated with etoposide since 1977 with a view to identifying the effect of this drug on fertility.

PATIENTS AND METHODS

Etoposide (VP16-213) an epipodophyllin derivative was introduced into our management protocol for middle and high risk gestational trophoblastic tumours in 1977 [6, 9]. Initially it was used in three patients alternating with CHAMOCA but later used in place of cyclophosphamide and vincristine in the sequential middle risk regimen and in the EMA/CO regimen for high risk patients (Table 1) [2]. All patients were advised to avoid getting pregnant for 12 months after completing chemotherapy.

Between 1977 and the end of June 1984, 204 women were treated using the various drug combinations described, either sequentially or simultaneously depending on the risk group. Twenty-one died from the disease or associated complications.

Detailed analysis of medical and obstetric history of the remaining 183 patients were performed and this was supplemented by questionnaires sent out where information was inadequate. Nineteen patients residing outside the United Kingdom could not be contacted while three patients living in this country failed to respond to the questionnaires sent. Up-to-date information was therefore available for 161 patients. Fifty-five patients had surgical sterilisation either in the form of total abdominal hysterectomy usually as part of the therapy or tubal ligation as a form of permanent contraception. Twenty-one other patients are using regular contraception. Eight patients did not recommence menstruation after the treatment and are classified as menopausal. Three patients who did not wish to conceive but did so had their pregnancies terminated. We present data on the 74 patients who wished to conceive following chemotherapy.

RESULTS

Of the 74 patients who wished to conceive, 66 (89.2%) succeeded with 57 (77.0%) having at least

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Table 1. *Treatment schedules for gestational choriocarcinoma*

	Cycling Regimen for Medium Risk Patients	
Consists of the following courses of chemotherapy which are given in the sequence shown below.		
(a)	Etoposide 100 mg/m^2 i.v. daily for 5 days.	
(b)	Hydroxyurea, 6-mercaptopurine (6mp), and methotrexate/ folinic acid (HuMMp)	
	Day 1	Hydroxyurea 500 mg p.o. 12-hourly for 2 doses
	Days 2,4,6,8,	MTX 50 mg i.m. at noon
	Days 3,5,7,9,	Folinic acid 6 mg i.m. at 6.00 p.m. 6.MP 75 mg P.O.
(c)	Actinomycin D 0.5 mg (total dose) i.v. for 5 consecutive days	
	The courses of therapy are given according to the following sequence with preferably drug free days kept to only 6 days	
1.	Etoposide	
2.	HuMMp	
3.	Actinomycin D	
4.	HuMMp	
5.	Etoposide	
6.	HuMMp	
7.	Actinomycin	
7.	HuMMp	
	If resistance develops the ineffective regimen is replaced by course d.	
(d)	Vincristine and Cyclophosphamide	
	Day 1,3,	Vincristine 0.8 mg/m^2 i.v.
	Day 1,3,	Cyclophosphamide 400 mg/m^2
	High Risk Patients (EMA/CO schedule)	
Course 1	Day 1,	Methotrexate 100 mg/m^2 i.v. stat. Methotrexate 200 mg/m^2 i.v. 12 hour infusion
	Day 1,2,	Actinomycin-D 0.5 mg i.v. stat. Etoposide 100 mg/m^2 i.v.
		Folinic acid 15 mg p.o./i.m b.d for 4 doses starting 24 hours after the start of methotrexate
	6-day drug free interval and if no mucositis	
Course 2	Day 1,	Vincristine 1.0 mg/m^2 i.v. stat. Cyclophosphamide 600 mg/m^2 i.v. 6-day drug free interval and if no mucositis
Course 1		as above 6-day drug free interval and if no mucositis
Course 2		as above
	Continue alternating courses of 1 and 2 until the patient is in complete remission or there is evidence of drug resistance.	

one live birth. At the time of analysis there were a total of 78 live births, 96 completed pregnancies and five ongoing pregnancies. In all eight (10.8%) patients who wished to conceive failed to do so. Two of these women had a previous history of infertility and ovulation induction. The average age of this group was comparable to those who succeeded in conceiving (Table 2). The mean dosage of etoposide was lowest in this group (1.3 g/m^2) and there was little difference in the duration of treatment between the groups (Table 2).

Eleven patients were aged 30 yr and above and wished to conceive. Nine (81.8%) succeeded but only seven (63.6%) had a live birth. The eight menopausal patients had a median age of 41 yr (range 30–47). The youngest menopausal patient

Table 2. Mean age, dosage, duration of treatment and interval between completion of treatment and pregnancy

Mean	(Number of patients in parentheses) At least one live birth	Conceived but no live birth	Failed to conceive	Menopausal patients
Age (yr)	25.2 (57)	25.6 (9)	26.2 (8)	40.3 (8)
Dosage of etoposide gm/m^2	1.52	2.1	1.3	1.7
Duration of treatment (weeks)	19.1	23.1	21.6	25.1
Interval from end of treatment to pregnancy (months)	20.8	23.6	32.6*	66*

*Mean follow-up period

had a right salpingo-oophorectomy performed for an ectopic pregnancy before her trophoblastic tumour and had 3.0 g/m^2 of etoposide over a total period of 73 weeks. She relapsed once after being in complete remission for 3 yr. In all 4 of the 50 patients in the middle risk group and 4 of the 24 in the high risk group have so far failed to get pregnant.

There were seven terminations, three for medical indications of severe hypertension, hydatidiform mole and missed abortions, 11 spontaneous abortions and one still birth following an intrauterine death at 39 weeks attributed to hypertension. Sixteen deliveries by caesarian section were done for various reasons. The miscarriage rate was 124/1000 with a caesarian section rate of 20.5%. The male to female ratio was 1.1 : 1.0. There was only one case of a twin delivery in a 20-year-old patient. She had a high risk post-mole gestational trophoblastic tumour and received the largest dosage of etoposide (4.8 g/m^2) in the series over a period of 65 weeks during which she relapsed once. There was only one case of congenital malformation, microcephaly possibly associated with cytomegalovirus infection *in utero*.

DISCUSSION

Gestational trophoblastic tumours are unique because of the age group of patients involved and the 90–95% survival among patients following developments over the years in the chemotherapy of the disease [1–3]. We have therefore an increasing proportion of women in their reproductive age group surviving and wanting to achieve conception and live births. Although these drugs are potential causes of gonadal dysfunction and may exert a mutagenic effect on the ova [11, 12], there is no evidence that currently available drug combinations impair fertility in patients with trophoblastic tumours [4, 13, 14].

Following the introduction of etoposide in 1977 as a potent anti-neoplastic agent in gestational trophoblastic tumours [5, 6], concern has been expressed about its gonadotoxic effect [8]. Our results show that out of 74 patients who tried to get pregnant after chemotherapy for gestational trophoblastic tumour, 57 (77.0%) succeeded in having at least one live birth and only eight (11.8%) did not conceive at all. When corrected for the two patients with a previous history of infertility, only six (8.1%) of the patients have true post chemotherapy infertility problems.

The group of those who succeeded in having at least one live birth is quite comparable to those who failed to get pregnant. The dosage of etoposide administered was lower for the infertile group which is against etoposide being the cause of the infertility. The oldest patient who had a live birth was 37 yr and all but one of the menopausal patients were older than 38 yr: 81.8% of patients above the age of 30 conceived and 63.6% had at least one live birth. This showed no difference in the ability of women over the age of 30 to conceive when compared with those under the age of 30. The retrospective nature of our study would however not permit us to determine if etoposide could accelerate the ovarian ageing process and hence cause premature menopause.

Unlike the single agent drug regimen used by Choo *et al.*, 1984, [8], etoposide was always given with other drugs either sequentially or in combination, thus the total etoposide dose was lower in our study. The highest dosage of 4.8 g/m^2 was administered to a 20-year-old patient who subsequently delivered twins 36 months after completion of chemotherapy.

The miscarriage rate was 124/1000 which was considerably lower than in our previous study [4]. The only perinatal death could not be attributed to the chemotherapy. Although potentially mutagenic

like all anti-neoplastic agents, there is no evidence that etoposide is teratogenic. In this series the only case of congenital abnormality was probably associated with cytomegalovirus infection.

Our study reveals that even though etoposide might have some temporary gonadotoxic effect, there is minimal long-term effect on fertility when it is given according to our currently used protocols for patients with gestational trophoblastic tumours.

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