Risk of Ovarian Failure and Fertility After Intravenous Cyclophosphamide. A Study in 84 Patients

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ABSTRACT. ***Objective.*** To compare the risk of ovarian failure and the fertility of women treated with intravenous cyclophosphamide (IVCY) according to the underlying inflammatory disease.

Methods. Review of the data of 84 consecutive women: 56 with systemic lupus erythematosus (SLE), 28 with other diseases, mainly Wegener's granulomatosis and systemic vasculitides.

Results. The mean age at IVCY initiation was 29 ± 10 years (range 13–53). The mean dosage was 0.9 ± 0.14 g per pulse (range 0.5–1), and the mean number of pulses 13 ± 6.5 (range 3–42). With a mean followup of 5.1 ± 3.7 years, 23 women developed amenorrhea, with a mean duration of 4 ± 3.6 months between IVCY initiation and amenorrhea. Amenorrhea was sustained in 19 women (13 with SLE and 6 with other diseases, NS). The mean age at ovarian failure onset was 40 ± 7.6 years. The risk of ovarian failure correlated with the age at IVCY institution ($p < 0.0001$), and was independent of underlying inflammatory disease. Eighteen women (13 with SLE and 5 with other diseases) became pregnant during or after CY therapy, with a total of 22 pregnancies. The mean age at IVCY initiation, and the mean number of IVCY (maximum 40 pulses) before pregnancy were similar in women with SLE and those with other diseases. Six pregnancies occurred during IVCY therapy, which ended in induced abortion (n = 3), spontaneous abortion (n = 1), and normal pregnancy after IVCY withdrawal (n = 2) in women who wished to keep their pregnancy despite the risk of teratogenicity. Sixteen pregnancies occurred 2.9 ± 2.1 years (range 1–9) after IVCY withdrawal. They ended in: 3 induced abortions indicated for severe morphological anomalies (n = 2) and for SLE relapse (n = 1), 3 spontaneous miscarriages, and 10 deliveries of healthy newborns.

Conclusion. The risk of ovarian failure depends essentially on the age at IVCY initiation. Pregnancy may occur during IVCY therapy, and an efficient contraception is mandatory. After IVCY withdrawal, pregnancy is possible with a favorable outcome in two-thirds of the cases. (J Rheumatol 2002;29:2571–6)

Key Indexing Terms:
OVARIAN FAILURE CYCLOPHOSPHAMIDE PREGNANCY
SYSTEMIC LUPUS ERYTHEMATOSUS SYSTEMIC VASCULITIS

Cyclophosphamide (CY) is an alkylating agent that damages DNA repair mechanisms with more impact on rapidly dividing cells. Its immunomodulatory effect, including suppression of T cell mediated immunity and reduction of antibody production, led to wide indications in inflammatory diseases, especially systemic lupus erythematosus (SLE). Ovarian failure is a well known side effect of CY therapy, with a cumulative incidence varying between 12% and 83%[1], depending on the underlying disease, use of concomitant drugs, particularly, chemotherapy, and mode of administration. Ovarian failure is a major concern in young women who have a high probability of survival[1-4]. Intravenous cyclosphosphamide (IVCY) pulse therapy is indicated in severe SLE, and also in other inflammatory diseases, where its benefit was often demonstrated in controlled studies[5-7]. In this setting, its impact on menses and fertility is not precisely known. We retrospectively analyzed the charts of 84 premenopausal women with SLE and other inflammatory diseases treated with IVCY therapy in order to determine risk of ovarian failure and fertility.

MATERIALS AND METHODS

Selection of patients. We reviewed the charts of all women below 55 years of age hospitalized in our internal medicine department to receive IVCY pulse therapy for inflammatory disease. Thirty-five patients treated before 1997 were studied retrospectively; and 49 patients followed since this date were studied prospectively. Two separate sources were used: a computerized hospital database in use over the last 5 years, and records of the internal medicine department for SLE, systemic vasculitis, and Behçet's disease. We excluded women in whom menopause had occurred before IVCY therapy, women with secondary amenorrhea of various causes (end stage renal disease, oophorectomy, pelvic irradiation, and hormone therapy such as progestogen or danazol), or with history of hysterectomy before IVCY initiation. Eighty-four women were identified as menstruating at IVCY initiation.

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Amenorrhea was defined as lack of menses for 4 months, and sustained amenorrhea as persistent amenorrhea for at least 12 months.

The following data were collected: demographic data; underlying disease; dates of IVCY initiation, amenorrhea, and pregnancy; CY pulse dosage; and number of IVCY pulses. When data on menses status were lacking, women were asked by phone. Data analysis was performed on Statview (1992–1998 SAS Institute Inc.). Chi-square test or Fisher's exact test were performed when required for all qualitative variables, and Student's t test for comparison of quantitative variables.

RESULTS

Fifty-six women had SLE. Indications of IVCY were: glomerulonephritis (n = 44), pulmonary hypertension (n = 5), central nervous system involvement (n = 3), thrombotic thrombocytopenic purpura (n = 1), corticosteroid resistant myositis (n = 1), and pleuritis (n = 2).

Twenty-eight women had other diseases. They consisted of Wegener's granulomatosis (n = 10), polyarteritis nodosa, micropolyangiitis, and Churg Strauss syndrome (n = 5), corticosteroid resistant Behçet's disease (n = 4), sarcoidosis (n = 3), Takayasu's arteritis (n = 2), idiopathic uveitis (n = 2), catastrophic antiphospholipid syndrome (n = 1), and relapsing polychondritis (n = 1).

The mean age at CY initiation was 29 ± 10 years (range 13–53). The mean IVCY dosage was 0.9 ± 0.14 g per pulse (range 0.5–1). The mean number of pulses was 13 ± 6.5 (range 3–42). The mean followup duration from IVCY initiation was 5.1 ± 3.7 years (range 6 mo–17 yrs).

Ovarian failure. Twenty-three women developed amenorrhea in the subsequent 1–12 months following IVCY initiation, with a mean lag of 4 ± 3.6 months. Amenorrhea was sustained in 19 women. The underlying diseases were SLE (n = 13), antiphosphospholipid syndrome (n = 1), Wegener's granulomatosis (n = 1), micropolyangiitis (n = 1), Churg Strauss syndrome (n = 1), sarcoidosis (n = 1), and Behçet's disease (n = 1). The mean age at ovarian failure onset was 40 ± 7.6 years. In comparison, the mean age at menopause is 51 years in France. The youngest woman was 28 years old, and amenorrhea occurred 2 months after IVCY initiation. Demographic data and IVCY regimen were similar in SLE and in the other diseases (Table 1). The risk of sustained amenorrhea depended more on the number of IVCY pulses and the age at IVCY initiation than on the underlying disease (Table 2). In SLE, the rate of ovarian failure was 12.1% when women were 30 years or less at IVCY initiation, and 39.1% when they were older. These rates were similar to those observed in the other inflammatory diseases: nil and 40%, respectively. The overall rate of ovarian failure was 15.8% when the number of pulses was 7 or less. It increased non-significantly to 20% when the number of pulses was 15 or more.

A woman with SLE developed menopause at the age of 38, i.e., 5 years after IVCY withdrawal. Another woman had irregular menses accompanied by elevated follicle stimulating hormone (FSH) at age 45 years, i.e., 7 years after IVCY cessation.

Comparison of features of women with SLE according to their menstruating status showed that women who developed sustained amenorrhea were older at SLE onset and at IVCY initiation. The lag elapsing between SLE onset and IVCY initiation was also shorter in women who developed sustained amenorrhea. The number of pulses, cumulative CY dosage, and duration of CY therapy were similar in the 2 groups (Table 3). Similarly, comparison of features of non-SLE women according to their menstrual status showed also that women who developed sustained amenorrhea were older at IVCY initiation (Table 4). Marital status, race, contraceptive pill use, indication of IVCY were similar in menstruating and in ovarian failure groups.

Pregnancy. Eighteen women became pregnant during or after IVCY therapy with a total of 22 pregnancies. Thirteen had SLE and 5 other inflammatory diseases. The mean age at IVCY initiation was 28 ± 5 years (range 20–35) in women with SLE, and 29 ± 6 years (range 20–35) in those with non-SLE diseases. The mean number of IVCY pulses received by each woman before pregnancy was 12.8 ± 9.1 (range 6–40) in women with SLE, and 13.5 ± 5.8 (range 9–18) in those with non-SLE diseases[5].

Six pregnancies occurred during IVCY therapy, despite intake of microprogestogen in one case. Pregnancy occurred after the 6th (n = 2), 7th (n = 1), 8th (n = 1), 16th (n = 1), and 17th (n = 1) pulses, respectively. Their outcomes were

Table 1. Main characteristics of premenopausal women treated with intravenous cyclophosphamide.

	SLE n = 56	Other Diseases n = 28	Total n = 84
IVCY			
Mean age at onset, yrs (range)	28 ± 9 (13–53)	30 ± 10 (14–50)	29 ± 10 (13–53)
Mean dosage per pulse, g (range)	0.9 ± 0.14 (0.5–1)	0.9 ± 0.12 (0.5–1)	0.9 ± 0.16 (0.5–1)
Mean No. of pulses (range)	12.8 ± 9 (3–42)	13.6 ± 5.3 (6–25)	13 ± 6.3 (3–42)
No. of sustained amenorrhea (%)	13 (23.2)	6 (21.4)	19 (22.6)
No. of pregnant women (%)	13 (23.6)	5 (17.8)	18 (21.6)

Table 2. Influence of the age at IVCY initiation on occurence of sustained amenorrhea after intravenous cyclophosphamide therapy.

Age at IVCY initiation, yrs	< 26	26 to 30	31 to 35	36 to 40	> 40
SLE Systemic lupus erythematosus, n = 56	0/13	4/20	1/9	4/7	4/7
≤ 7 pulses	0/5	0/1	0/3	2/4	1/4
≥ 8 pulses	0/8	4/19	1/6	2/3	3/3
Other diseases, n = 28	0/9	0/4	0/9	1/1	5/5
≤ 7 pulses	0/1	0/1	0/1	1/1	0/0
≥ 8 pulses	0/8	0/3	0/8	0/0	5/5
Total, n = 84	0/22	4/24	1/18	5/8	9/12

Table 3. Main characteristics of women with SLE according to the menstrual status after intravenous cyclophosphamide therapy.

	Ovarian Failure, n = 13	Menstruating, n = 43	p
Age at IVCY initiation, yrs (range)	37 ± 7 (30–53)	26 ± 8 (13–45)	< 0.0001
Age at SLE onset, yrs (range)	28 ± 9 (10–42)	22 ± 8 (10–39)	0.03
SLE duration, yrs (range)	9 ± 5 (2–20)	3 ± 3 (0–13)	< 0.0001
Never married (%)	3 (23)	25 (58.1)	0.057
Contraceptive pill use (%)	6 (46)	20 (46.5)	NS
Origin (%)			
Metropolitan French	8 (61.5)	18 (41.9)	NS
West Indian	1 (7.7)	5 (11.6)	
Northern Africa	2 (15.4)	9 (20.9)	
Other	2 (15.4)	11 (25.6)	
Indications of IVCY therapy			
Glomerulonephritis	8 (61.5)	36 (83.7)	NS
CNS involvement	0	3 (7)	
Pulmonary hypertension	2 (15.4)	3 (7)	
Other	3 (23.1)	1 (2.3)	
Mean IVCY dose per pulse, g (range)	0.93 ± 0.15 (0.75–1)	0.92 ± 0.16 (0.5–1)	NS
No. of IVCY pulses (range)	13.7 ± 7.3 (6–23)	12.6 ± 7.1 (3–40)	NS
Total cumulative IVCY dose, g (range)	11.3 ± 7.3 (6–23)	11.7 ± 6.1 (3–28 g)	NS
Duration of IVCY therapy, yrs (range)	1.5 ± 1 (0.5–2.5)	1.1 ± 1.1 (0.3–4)	NS

as follows: therapeutic abortion (n = 3), spontaneous abortion at 12 weeks of gestation (n = 1), and live birth (n = 2) in 2 women who wished to keep the pregnancy despite the risk of teratogenicity. In these last 2 pregnancies, occurring in women with SLE with glomerulonephritis, conception occurred 6 weeks and 8 weeks, respectively, after the last IVCY pulse. IVCY was stopped and corticosteroids were maintained at the same dosage of 20 and 10 mg daily until delivery, without SLE flare. No anomaly was observed in the children.

Sixteen pregnancies occurred in 9 women after IVCY withdrawal, with a mean lag of 2.9 ± 2.1 years (range 1–9) between therapy withdrawal and pregnancy. During IVCY therapy, 6 women had no contraception, 2 had an intrauterine contraceptive device, and 1 received a microprogestogen containing pill. Three pregnancies ended in therapeutic abortion for severe morphological anomaly (n = 2), or for SLE relapse (n = 1). Three spontaneous miscarriages occurred, 2 occurring early and one at 15 weeks gestation. Ten pregnancies ended in premature (n = 7) and full term (n = 3) deliveries of healthy newborns. No child had congenital malformation. Table 5 gives the number of pulses and the age at IVCY onset for these 18 women.

Table 4. Main characteristics of women with underlying inflammatory disease other than SLE according to the menstrual status after intravenous cyclophosphamide therapy.

	Ovarian Failure, n = 6	Menstruating, n = 22	p
Age at IVCY initiation, yrs (range)	45 ± 3 years (40–50 years)	26 ± 7 years (14–35 years)	< 0.0001
Never married (%)	2 (33)	13 (59)	NS
Contraceptive pill use (%)	0	10 (45)	NS
Origin (%)			
Metropolitan French	4 (66.7)	17 (77.3)	NS
Other	2 (33.3)	5 (22.7)	
Indications (%)			
Systemic vasculitis	3 (50)	14 (63.6)	NS
Other	3 (50)	8 (36.4)	
Mean IVCY dose per pulse, g (range)	1 g (1 g)	0.93 ± 0.1 g (0.5–1 g)	NS
No. of IVCY pulses, (range)	12.8 ± 6.7 (7–14)	13.9 ± 5 (6–15)	NS
Total cumulative IVCY dose, g (range)	12.8 ± 6.7 (7–14)	12.8 ± 4.8 (6–19)	NS
Duration of IVCY therapy, yrs (range)	1.06 ± 0.5 (0.5–2)	1.2 ± 0.4 (0.2–2.08)	NS

Table 5. Number of cyclophosphamide pulses and age at cyclophosphamide therapy initiation in 18 women who became pregnant during or after intravenous cyclophosphamide therapy.

	< 26 yrs	26 to 30 yrs	> 30 yrs
SLE n = 13	5	4	4
≤ 7 pulses	0	1	2
≥ 8 pulses	5	3	2
Other diseases, n = 5	1	2	2
≤ 7 pulses	0	1	0
≥ 8 pulses	1	1	2
Total, n = 18	6	6	6

DISCUSSION

In our retrospective study, we found a frequency of sustained amenorrhea after IVCY therapy of 22.3%. This rate is similar to that observed in 3 prior studies analyzing the impact of CY therapy on menses in SLE (Table 6). In the United States, Boumpas[3] found a 35.9% rate of amenorrhea, (28% of which were sustained). In this study, there was a trend towards higher rate of sustained amenorrhea in women treated with 15 or more IVCY pulses: 39% versus 12% in patients treated with 7 IVCY pulses (p = 0.07). In the United Kingdom, McDermott and Powell[1] found a 54% rate of ovarian failure. However, in this study, the mean age at IVCY initiation was higher than in the other studies. In Hong Kong, Mok[2] observed that the overall rate of ovarian failure was 30% in 54 women treated orally, and 13% in 16 treated intravenously with CY. Amenorrhea could be directly attributed to IVCY therapy since it was not observed in SLE controls treated with methylprednisolone pulses[3]. The rate of amenorrhea was also significantly higher than in SLE women treated with azathioprine and in healthy controls[1].

In our study, the age at IVCY initiation appeared the main indicator for ovarian failure. The rate of sustained amenorrhea was nil at 25 years or less, and it increased to 45% at 31 years or more, and was 83.3% over 40 years. This fact was also observed by 3 previous studies. In Boumpas's study[3], the rate of sustained amenorrhea was 12% at 25 years or less, and 62% at 31 years or more. It was 14% before the age of 30 years, and increased up to 50% at 40 years or more in Mok's study[2]. In McDermott and Powell's study[1], the rate was 44% before 40 years of age. The incidence of ovarian failure increased in a linear trend with the age at IVCY initiation. In our study, the risk of sustained amenorrhea was similar whatever the number of IVCY pulses administered: it was 15.8% for 7 pulses or less, and it increased not significantly to 24.2% for 8 or more IVCY pulses. In Boumpas's study[3], the rate of sustained amenorrhea was 12% for 7 pulses or less, and 39% for at least 15 pulses, and this was not significant (p = 0.07). For McDermott and Powell[1], duration of treatment was predictive of development of ovarian failure, but not mean dose of IVCY pulse, or mean IVCY cumulative dose. On the other hand, Mok found that the cumulative dose of CY, whether administered orally or IV, was significantly higher in women who developed ovarian failure, than in those menstruating. However, in our study, mean IVCY dose per pulse, cumulative dosage, and duration of IVCY therapy were similar in patients who developed sustained amenorrhea and those who continued menstruating (Tables 3 and 4). When our results were compiled with those of Boumpas's study, there was no significant increase of

Table 6. Rate of ovarian failure after cyclophosphamide therapy in inflammatory diseases in the literature.

Authors, Date No. of Patients	CY Administration	Diseases	Rate of Ovarian Failure (%)
Boumpas, et al, 1993[3], n = 39	IV	SLE	11 (28.2)
McDermott and Powell, 1996[1], n = 35	IV	SLE	19 (54)
Mok et al, 1999[2]			
n = 54	Oral	SLE	16 (30)
n = 16	IV	SLE	2 (16)
Our study, n = 84	IV	SLE and non-SLE	19 (22.6)

ovarian failure rate when the number of pulses increased (Table 7). In accord with McDermott and Powell's study[1], we found that the marital status (ever or never married) slightly correlated with ovarian failure (p = 0.057) only in women with SLE, with a greater rate of ovarian failure in married women. This was probably due to higher age at IVCY initiation, since SLE appeared less severe in older patients, and since the married women were older. We found that SLE duration was greater in women who developed ovarian failure, but this indicator did not appear to be significant in McDermott and Powell's study[1]. Other indicators tested by these authors also did not appear significantly associated with amenorrhea, i.e., smoking status, occupation, racial group, age of menarche, and parity[1].

In our series, occurrence of ovarian failure appeared independent of underlying disease. A higher frequency of ovarian failure under IVCY could have been expected in SLE, because of the addition of risk of autoimmune premature ovarian failure to the risk of CY-induced ovarian failure. Diagnosis of premature ovarian failure is based on amenorrhea of at least 4 months with persistent elevated FSH levels before the age of 40 years. Premature ovarian failure is frequently associated with autoimmune anomalies. In an Italian series, premature ovarian failure was considered idiopathic in 52.5% of the cases, chromosomal in 2.5%, while in 45% the cause was thought immunological because of positive autoantibodies (antithyroid microsomal in 27.5%, antinuclear in 20%, and antithyroid globulin antibodies in 12.5% of the cases)[8]. Serum antibodies to ovarian and other self-tissue were found in up to one-third of women with premature ovarian failure. Autoimmune premature ovarian failure can occur as an isolated event, or be part of the genetic disorder named the polyglandular autoimmune syndrome type I, or be associated with other autoimmune diseases. In SLE, anti-ovary autoantibodies were demonstrated in 19 of 87 women less than 40 years of age[9].

Table 7. Absence of correlation between ovarian failure and number of cyclophosphamide pulses. Compiled data.

	≤ 7 pulses	≥ 8 pulses
Boumpas, et al[3], n = 39	2/16	9/23
Our study, n = 84	4/21	15/74
Total, n = 123	6/37	24/86

In our series, use of contraceptive pill containing only progestogen was similar in SLE women developing sustained amenorrhea, and in those menstruating. Several approaches were proposed to preserve ovarian function during CY therapy. The protective effect of oral contraceptives was suggested based on a small series of 6 young women with Hodgkin's disease undergoing chemotherapy[10]. However, estrogen containing contraceptive is classically contraindicated in SLE, owing to risk of flare[11,12]. Recently, Blumenfeld[13] studied the effect of buserelin in prevention of hypergonadotropic amenorrhea in 17 women with autoimmune disease undergoing chemotherapy (CY or chlorambucil). Although the study was short and not controlled, it suggested a protective effect of buserelin, since none of the 8 women treated with buserelin developed premature ovarian failure versus 5 of 9 untreated women. Chlormadinone (2 mg daily for 21 days) could also preserve ovarian function: in a double blind controlled trial in 61 patients with SLE nephritis treated with IVCY, serum luteinizing hormone and FSH levels were significantly lower, and estradiol level significantly higher at 12 months in women treated with chlormadinone, compared with those treated with placebo. The rate of ovarian failure was also lower: it occurred in 4 of 31 women treated with chlormadinone, versus 8 of 28 treated with placebo[14].

We observed 6 pregnancies during IVCY therapy, leading to premature withdrawal of immunosuppressive therapy. Fortunately, pregnancy diagnosis was made early and cytotoxic therapy stopped. Three women wanted to keep the pregnancy, which ended in one early spontaneous miscarriage and 2 normal live births. CY is clearly teratogenic in animals, producing central nervous system, facial, and skeletal anomalies in mice, rats, rabbits, and monkeys[15]. In humans, 11 cases of congenital anomalies after a first trimester exposure have been published, but most reports of congenital malformation were related to combination of CY and radiotherapy or other chemotherapy.

CY crosses the placenta. Its amniotic fluid concentration is about 25% the plasma level[15]. To our knowledge, only 4 reports of pregnancy arising in SLE under IVCY therapy are available. One ended in therapeutic abortion because of possible teratogenicity[16]. Two pregnancies with first

trimester IVCY *in utero* exposure ended in live birth with multiple anomalies[15,17]. In the first case, the mother received 200 mg IVCY on days 15 and 46 of gestational age[17]. In the second case, the mother received 20 mg/kg IVCY on day 37. Congenital anomalies were similar, consisting of microcephaly, malformations of ears and eyes, hypoplastic thumbs, suggesting a distinct embryopathy[15]. One pregnancy, which began 10 days after the last IVCY pulse, ended in normal live birth[16]. Use of CY in the second and third trimesters seemed to be free of congenital anomalies[18-21]. We did not observe any case of congenital malformation when pregnancy occurred after IVCY therapy withdrawal. The longterm effect of CY on pregnancy is not known. Ramsey-Goldman[22] analyzed the outcome of 23 pregnancies occurring in women treated with immunosuppressive treatment (CY, methotrexate, or azathioprine) prior or during pregnancy, and 113 pregnancies with no exposure to immunosuppressive therapy. The rate of adverse pregnancy outcome (premature delivery, growth restriction, spontaneous abortion) was similar in the 2 groups. There was no congenital malformation in infants exposed to azathioprine during pregnancy.

In conclusion, risk of ovarian failure correlates with the age at IVCY initiation, and is independent of the underlying inflammatory disease. Pregnancy may occur during IVCY therapy, and an efficient contraception is mandatory. After IVCY withdrawal, pregnancy is possible with a favorable outcome in two-thirds of the cases.

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