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Paternity in Patients with Testicular Germ Cell Cancer: Pretreatment and Post-treatment Findings

Peter Vejby Hansen, Karin Glavind, Jytte Panduro and Mogens Pedersen

Paternity before and after treatment was investigated in 177 patients with unilateral germ cell tumours of the testis. Before the cancer was diagnosed, 51% had fathered at least 1 child, 9% had a history of infertility and 40% had not wanted to have children. It was estimated that 72% of the patients would have fathered at least 1 child at the age of 40 years. After treatment 41 patients had wished to have children. Infertility was still a problem 5 years after the end of treatment in 53% of these men. No significant differences was observed between patients treated with orchiectomy alone and patients treated with cisplatin-based chemotherapy or subdiaphragmatic irradiation. In 8 patients, infertility was present in spite of an evident recovery of spermatogenesis. Congenital malformations were recorded in 3.8% of the live-born children conceived before the orchiectomy. This incidence did not exceed the Danish national rate, the relative risk being 2.5 (95% confidence limits, 0.9–5.5). No malformations were observed in the 22 children conceived after ending treatment.
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INTRODUCTION

THE LONG-TERM survival of patients with germ cell tumours of the testis is increasing [1]. Attention has therefore shifted to the physical and psychological consequences of the disease itself and its treatment, and to the question of fertility. The low postorchiectomy sperm counts in testicular cancer patients may in some cases be explained by a history of cryptorchidism or carcinoma *in situ* of the contralateral testis [2, 3]. In most patients, however, the origins of this impairment remains unknown [2]. Gonadal dysfunction should be expected to have impaired fertility before the cancer was actually diagnosed. Treatment with combination chemotherapy and radiotherapy can further impair the spermatogenesis, but sperm production seems to resume in most patients treated for testicular cancer [4, 5]. Prior studies on the paternity before treatment comprise small and selected groups, and little information is available about the actual fertility after treatment [6]. No information is available concerning children fathered prior to the orchiectomy [6], and data on children fathered after treatment are few [7, 8].

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The aim of the present study was to describe paternity before and after treatment in a representative group of patients with testicular germ cell cancer. Conception of live-born children before and after treatment was investigated in patients with testicular cancer diagnosed in one county in a 10-year period.

PATIENTS AND METHODS

Patients

In the 10-year period from January 1977 to December 1986, 186 consecutive patients with unilateral testicular germ cell cancer were recorded in the county of Northern Jutland, Denmark. After orchiectomy all patients were referred to the Department of Oncology in Aalborg. 1 patient with severe mental deficiency and 1 patient with paralysis caused by poliomyelitis were excluded from the study. 3 seminoma patients and 4 non-seminoma patients declined to participate. The remaining 177 patients gave informed consent according to the guidelines given in the Declaration of Helsinki. 3 of these patients developed a contralateral testicular cancer, 13 patients had progressive disease, and 3 patients migrated. These 19 men were not evaluated for post-treatment paternity. The median observation period after discontinuation of treatment of the remaining 158 patients was 4 years (range 1–10). 97 patients were also included in an investigation of testicular function. These results are mainly reported elsewhere [9–11], but some sperm count data have been included in the present study.

Interviews

Patients answered standardised questionnaires both at referral to the Department of Oncology and at clinical routine follow-ups at the hospital. The patients were asked if they had fathered live-born children before or after treatment, and if not whether infertility was voluntary. When possible, the length of the period of infertility was noted. End-points related to male fertility were defined as described by Eliasson [12]. For each child, the sex, the date of birth and the medical history were noted. The children were not examined. Data therefore only include disorders causing hospitalisation. Data on abortions were not recorded.

Statistical methods

The Mann–Whitney test was used for comparison of groups of observations. Confidence intervals were generated for probabilities by assuming a binomial distribution. Kaplan–Meier estimates were calculated to illustrate the cumulative probability of conception of a live-born child. As the exact time of conception was unknown, a pregnancy duration of 282 days was assumed in the calculations. Estimated values are specified with 95% confidence limits in brackets. The Kaplan–Meier estimates were compared by the logrank test. The joint influence of the various factors was assessed by the proportional hazard model proposed by Cox [13]. A significance level of 0.05 was employed.

RESULTS

Clinical characteristics and paternity before the cancer was diagnosed are given in Table 1. 40% of the patients had not attempted conception, 51% had fathered from 1 to 4 children, and 9% of the men had a barren union. Kaplan–Meier estimates showing the relationships between the father's age at conception and the cumulative percentage of men who had conceived 1 live-born child pre-orchiectomy are shown in Fig. 1. 7 patients declined to state the date of birth of their children, and they were therefore excluded from the calculations. At the age of 40 years, it was estimated that 72% (62–82%) of the remaining 170 patients would have fathered at least 1 child. The corresponding estimate for the 100 patients who wanted to have children was 88% (80–96%). The influence of patient characteristics on the cumulative probability of conception of 1 child was investigated in this group of patients (3 men with infertile partners excluded). Neither the univariate analysis nor the Cox regression analysis revealed any significant effect of histological type, prior cryptorchidism, inguinal hernia, or other genital conditions ($P > 0.05$).

88 men had fathered a total of 169 live-born children before

Table 1. Clinical characteristics and paternity before the cancer was diagnosed in 177 patients with testicular cancer

	Seminoma (n = 87)	Non-seminoma (n = 90)	Total (n = 177)
Median age (yr) (range)*	39 (20–75)	27 (16–55)	32 (16–75)
Cryptorchidism†	6 (7)	8 (9)	14 (8)
Inguinal hernia†	15 (17)	8 (9)	23 (13)
Genital conditions†	8 (9)	2 (3)	10 (6)
Paternity	17 (20)	53 (59)	70 (40)
Not attempted conception			
Infertile couples‡	14 (16)	2 (2)	16 (9)
Father before treatment	56 (64)	35 (39)	91 (51)
No. of children			
One	13 (23)	12 (34)	25 (28)
Two	29 (52)	16 (46)	45 (49)
Three or more	13 (23)	5 (14)	18 (20)
Unknown	1 (2)	2 (6)	3 (3)
Male children§	49 (46)	24 (47)	73 (47)
Malformations§	2 (2)	4 (8)	6 (3)
Paediatric disorders§	3 (3)	2 (4)	5 (3)

No. of patients (%).
*Age at orchiectomy.
†Cryptorchidism (ipsilateral testis in 8 patients, contralateral testis in 4 patients, and bilaterally in 2 patients) and inguinal hernia from 176 cases with a known variable; genital conditions (mumps orchitis in 5 patients, hydrocele and/or varicocele and/or spermatocele in 5 patients) from 166 cases.
‡Includes 3 couples with known female infertility.
§Sex, malformation and paediatric disorders in 157 children.

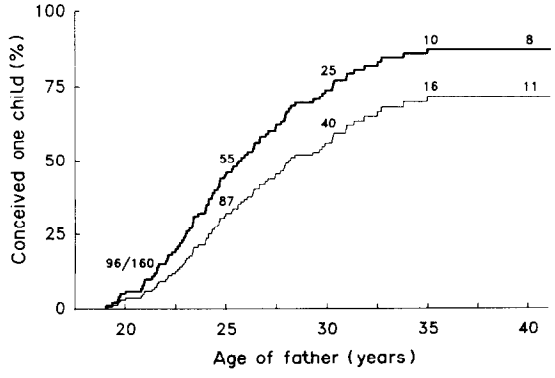

Fig. 1. Relation between age of father at conception and the cumulative percentage of patients who had conceived 1 child pretreatment. —— = 170 patients with known date variables, —— = 100 patients who attempted conception. Figures indicate number of patients at risk.

*Table 2. Treatment characteristics and paternity after treatment in 158 patients with testicular cancer**

	Orchiectomy alone (n = 45)	Chemo-therapy (n = 28)	Radio-therapy (n = 85)	Total (n = 158)
Median age (yr) (range)†	38 (22–73)	31 (21–58)	41 (24–78)	38 (21–78)
Not attempted conception				
Father pretreatment	23 (51)	5 (18)	41 (48)	69 (44)
Pretreatment infertility	3 (7)	1 (3)	2 (2)	6 (4)
Never attempted	10 (22)	14 (50)	18 (21)	42 (26)
Attempted conception				
Infertile couples‡	6 (13)	5 (18)	14 (17)	25 (16)
Father post-treatment§	3 (7)	3 (11)	10 (12)	16 (10)

No. of patients (%).
*19 patients analysed for pre-treatment fertility are not included due to contralateral testicular cancer (3 patients), progressive disease (13) and migration (3).
†Age at day of latest interview.
‡Includes 5 couples with known female infertility.
§10 patients fathered 1 child and 6 patients fathered 2 children. A further 3 children were conceived by cryopreserved semen (figures not included).

the orchiectomy (Table 1). Another 3 men had fathered an unknown number of children. Detailed information was available in 157 of these children. The proportion of boys [46.5 (38.6–54.7)%] was not different from the expected 51.4% [14]. Congenital malformations were recorded in 6 children fathered by 5 men: hydrocephalus, bilateral hip joint dislocation, mental deficiency and other malformations, septal heart defect, multiple congenital malformations, cleft lip and palate and other malformations. The figure of 3.8% (1.4–8.2%) did not significantly exceed the incidence of 1.5% in the general population [14], the relative risk being 2.5 (0.9–5.5). A history of a severe paediatric disorder was recorded in another 5 children: brain tumour (2 cases), psychiatric disorder, kidney disease and deafness.

Paternity after treatment is illustrated in Table 2. 16 patients had conceived 22 healthy children at a median of 5 years (range from end of treatment to 9 years) after discontinuation of treatment. 25 patients who attempted conception remained infertile at a median of 4 years (range 1–10 years) after treatment. At the latest interview, 42 patients [26% (20–34%)] who had never attempted to conceive were alive without recurrence.

Kaplan–Meier estimates of the time from the end of treatment until conception of 1 child are given in Fig. 2. The data show that 15% (7–23%) of the men would have fathered 1 child within 5 years and 21% (9–33%) within 10 years after treatment. The corresponding estimates for the 41 patients who wished to have children were 47% (27–67%) and 64% (38–90%). The estimates for different treatment groups were compared for patients who attempted to conceive (5 men with infertile partners excluded). There were no significant differences between patients treated with orchiectomy alone, patients treated with PVB or patients treated with subdiaphragmatic irradiation ($P > 0.05$). Post-treatment sperm count data were available in 25 of these patients. 10 fathers had delivered semen samples within 6 months before or after conception of their first child post-treatment (Fig. 3, left panel). The maximal total sperm count per ejaculate observed

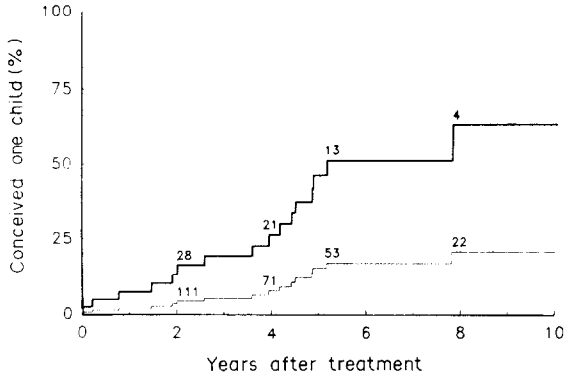

Fig. 2. Relation between the time after treatment and the cumulative percentage of patients who had conceived 1 child post-treatment. —— = 158 patients with known variables, —— = 41 patients who attempted conception.

during the period of infertility in 15 patients with a barren union is also presented in Fig. 3 (right panel).

Cryopreservation of semen was performed prior to treatment in 11 of the patients who attempted to conceive after treatment. Conception was achieved in 3 of 5 couples where inseminations were performed. The children (2 girls, 1 boy) were healthy. These 3 children are not included in the life tables.

DISCUSSION

Data on the fertility of patients with testicular germ cell cancer are sparse. Although the effects of the disease itself and its treatment on the spermatogenesis have been thoroughly investigated, most reports provide little information on the details of paternity and seldom give data on the offspring [6]. The subnormal level of the sperm counts in patients with testicular cancer after unilateral orchiectomy can in part be explained by (1) the loss of half of the seminiferous epithelium [15]; (2) a reversible reduction of sperm production due to the cancer [2, 9]; and (3) the arrest of spermatogenesis because of cryptorchid-

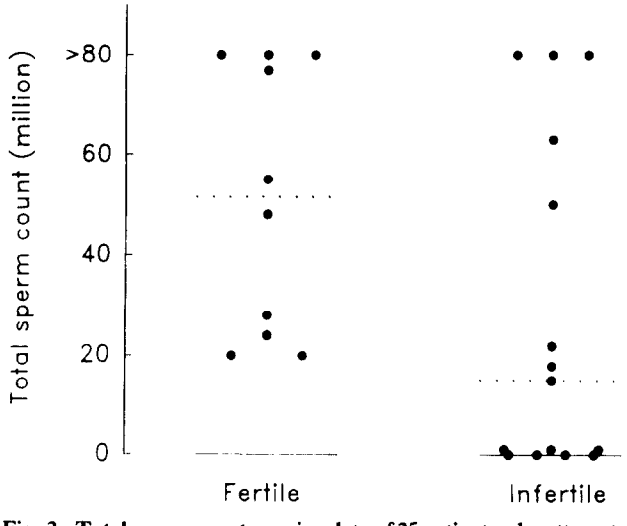

Fig. 3. Total sperm count per ejaculate of 25 patients who attempted conception after the end of treatment. Left panel = data from 10 fathers. The samples were obtained within 6 months before or after conception of their first child post-treatment. Right panel = maximal value observed during the period of post-treatment infertility in 15 patients with a barren union. Dotted lines indicate median values.

ism or carcinoma *in situ* of the contralateral testis [2, 3, 16]. In most patients, however, the reasons for the low sperm counts are unknown. It remains to be clarified whether the dysfunctioning after the orchiectomy actually coincides with a reduced paternity before the cancer was diagnosed [6, 17].

Before the orchiectomy, 51% of the current patients had fathered at least 1 child, whereas 9% of the men had experienced a barren union. These results are in accordance with those reported by others [6, 18, 19]. In order to describe the fertility rate, the time needed for conception in each couple should be recorded. The pretreatment fertility data, however, were not ideally accurate because most patients could neither state the length of the infertility period nor could they exactly recollect the events during this period at the time of the interview. Furthermore, the age and previous family histories of the patients affect the probability of having children [18], and 40% of the current patients had not attempted to conceive before the orchiectomy. The time relationship of conception was therefore based on the age of the father. We estimated that 72% (62–82%) of the patients would have fathered at least 1 child at the age of 40 years. The specific paternity rate in Denmark is unknown at present (L. Knudsen, Danmarks Statistik), whereas 90% of Danish women had at least 1 live birth at the age of 40 years [20]. If the reproduction rate of the general male population is at a comparable range, the paternity rate seems considerably reduced in men who develop testicular cancer.

The investigation of the testicular function [9–11] included most of the men who wanted to conceive after the treatment. They were advised not to attempt conception within the first year, but most, knowing that they were azoospermic, used no contraceptives in defiance of these recommendations. Time after treatment and not time of intended conception therefore reflected the time-at-risk when no contraceptives were used. 53% of the men who wished to father a child were still infertile 5 years after the end of treatment, a percentage which is in agreement with previous reports [6]. There was no statistically significant difference between patients treated with orchiectomy alone and patients who also received radiotherapy or chemotherapy. The number of patients in each treatment group, however, is small. Temporary azoospermia is probably induced in all patients during subdiaphragmatic irradiation or treatment with cisplatin-based chemotherapy, but spermatogenesis seems to recover with time in most patients [4, 5, 10, 11]. The present study confirmed that conception may take place during the recovery period although the sperm counts are low [7]. We also observed infertility in 8 patients with an evident recovery of sperm production. This may be due to treatment-induced damage to the spermatogenesis or reflect the low frequency of sexual activity observed in some patients treated for testicular cancer [21–23]. However, this finding also conforms with statements that semen samples with a sperm density of 5 millions/ml or higher do not discriminate fertile from infertile men [12].

In order to evaluate whether the diagnoses and treatment of a testicular cancer reduce the expected "life-paternity-rate", we calculated Kaplan–Meier estimates for the combined pre-treatment and post-treatment paternity data. Conception of 1 live-born child was used as an end-point. At the age of 40 years, it was estimated that 82% (74–90%) of the patients who attempted conception before or after treatment [66% (58–74%) of the total number of patients] would be a father. These figures were not significantly different from the corresponding pretreatment estimates of 88% (80–96%) and 72% (62–92%), respectively.

The issue of malformations in children fathered by testicular cancer patients before the cancer was actually diagnosed have not been reported before [6]. The current study observed no increase in the incidence of congenital malformations in live-born children fathered before the orchiectomy. The children were not examined, and hence the number of malformations recorded was probably lower than the actual number. Furthermore, these children represent different birth cohorts and comparison with the present Danish incidence may therefore be dubious. In agreement with previous reports [6–8, 18, 24–27], we observed no indications of an increased incidence of malformations in children fathered by men treated with subdiaphragmatic irradiation and/or chemotherapy [0% (0–15%)].

In conclusion, it was estimated that 72% of the testicular cancer patients would have fathered at least 1 child pretreatment at the age of 40 years. Infertility was still a problem 5 years after treatment in 53% of patients who wished to father a child. No difference was observed between patients under surveillance and patients who were also treated with chemotherapy or radiotherapy. The incidence of congenital malformations was not increased in children conceived before or after treatment. Paternity seems to be reduced in patients with testicular germ cell cancer, but more knowledge on the reproduction rate in the general male population is needed to clarify this issue.

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Testicular Dysfunction in Hodgkin's Disease Before and After Treatment

S. Viviani, G. Ragni, A. Santoro, L. Perotti, E. Caccamo, E. Negretti, P. Valagussa and G. Bonadonna

Over a 7-year period, semen analysis was performed in 92 male patients with Hodgkin's disease prior to therapy. In 67% of patients semen revealed a decreased chance for fertility (i.e. oligozoospermia, asthenozoospermia and/or teratozoospermia). The mean basal levels of follicle-stimulating hormone (FSH), luteinising hormone, testosterone and prolactin were in the normal range. In 77 patients in complete remission after alternating MOPP/ABVD (mechlorethamine, vincristine, procarbazine, prednisone; doxorubicin, bleomycin, vinblastine, dacarbazine), testicular function was assessed. 87% of patients were azoospermic, 9% had semen abnormalities and only 4% were normospermic. Recovery of spermatogenesis was documented in only 17 of 42 (40%) reassessed patients after a median time of 27 months and was generally not affected by pretreatment sperm quality. After chemotherapy, the mean value of FSH [20.45 (S.E. 1.7) mUI/ml] was significantly superior compared with that of the mean pretreatment values. No difference was documented in the mean testosterone and prolactin values tested before and after treatment. Our findings indicate that, of patients with Hodgkin's disease, about half are affected by hypogonadism before starting chemotherapy. By utilising alternating MOPP/ABVD, persistent testicular dysfunction was documented in half of the patients.
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INTRODUCTION

DURING THE past years, many efforts have been made to identify treatments devoid of organ damage such as gonadal failure, which may affect considerably the quality of life in young patients with Hodgkin's disease. Several reports [1–6] have indicated that MOPP (mechlorethamine, vincristine, procarbazine and prednisone) or MOPP-like combinations, i.e. those including a classical alkylating agent and/or procarbazine, induce testicular damage in about 90% of patients. In fact, mechlorethamine and procarbazine have long been considered the responsible agents for germ cell toxicity. A comparative analysis of MOPP and ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) showed permanent gonadal dysfunction only in patients treated with MOPP [7]. The damage of gonadal function induced by cytotoxic drugs is not the only cause of the sexual abnormalities in Hodgkin's disease. Chapman *et al.* [8] reported that gonadal abnormalities may exist in men with Hodgkin's disease before therapy. Furthermore, it has been suggested [9] that hypogonadism in untreated patients with Hodgkin's disease is not simply due to primary testicular failure, but is probably dependent upon a complex abnormality also involving the hypothalamic–pituitary axis, as suggested by the evidence of increased basal levels of prolactin. These abnormalities may be due to an altered dopaminergic tone at hypothalamic sites [8, 9].

The present study was carried out to assess testicular dysfunction in patients with Hodgkin's disease before and after treatment with alternating MOPP/ABVD.

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