original paper

haematologica 2001; 86:624-628
http://www.haematologica.it/2001_06/0624.htm

Successful pregnancies following an egg donation program in women with previously treated Hodgkin's disease

ANNA PAOLA ANSELMO, ELENA CAVALIERI,* CESARE ARAGONA, MARCO SBRACIA,* DARIA FUNARO, RICCARDO MAURIZI ENRICI°
Dipartimento di Biotecnologie Cellulari ed Ematologia, *Sterility Unit II Obstetrics and Ginecology, °Istituto di Radioterapia Università "La Sapienza", Rome, Italy

Correspondence: Anna Paola Anselmo, M.D., Dipartimento Biotecnologie Cellulari ed Ematologia Università "La Sapienza", via Benevento, 6, 00161 Rome, Italy. Phone: international +39-06-857951
Fax: international +39-06-44241984
E-mail: anselmo@bce.med.uniroma1.it

Background and Objectives. In order to draw attention not only to patients affected by a neoplasia, but also to those who may have problems of sterility, we describe six women affected by Hodgkin's disease who had precocious menopause due to chemotherapy and/or radiotherapy but who were safely delivered of children. These pregnancies were achieved through oocyte donation, *in vitro* fertilization and intrauterine embryo transfer or oocyte intracytoplasmic insemination.

Design and Methods. During natural or iatrogenic menopause, the uterus preserves its capacity to respond to steroidal hormones and to permit implantation and development of an embryo. Our study concerns six young females with iatrogenic menopause caused by treatment of Hodgkin's disease who carried a pregnancy to term. The pregnancies were achieved by oocyte donation, *in vitro* fertilization and intrauterine embryo transfer or oocyte intracytoplasmic insemination. Endometrial maturation was obtained by administration of estradiol and progesterone. Steroidal therapy was administered until the 13th-14th week in relation to placental function.

Results. Five of the 6 females underwent Caesarean section because of a twin birth or complications during the third trimester of pregnancy (gestosis). All the delivered children are, to date, well; their median age is 4 years.

Interpretation and Conclusions. This study confirms the possibility of women treated for Hodkin's disease being able to carry a pregnancy safely to term with the help of steroidal therapy. Careful clinical and obstetric surveillance is important. Focusing attention on long-term survivors of Hodgkin's disease, we set the goal of improving the quality of life of these patients, considering their psychophysical well-being as a whole. Greater attention to the problems of safeguarding fertility in these patients would be advisable, also in the light of legislative regulation of medical care techniques in various countries.

Key-words: egg donation, Hogdkin's disease, iatrogenic menopause, pregnancy, sterility

About 60-70% of patients affected by Hodgkin's disease achieve recovery. The encouraging results in terms of prognosis have allowed attention to be turned to long-term physical and psychosocial sequelae of treatment.[1] In fact, some protocols, above all those including alkylating drugs and subdiaphragmatic radiotherapy, produced gonadal damage: azoospermia in men and precocious menopause in women. In particular, patients with advanced and subdiaphragmatic Hodgkin's disease have a high risk of becoming sterile.[2] The damaging effect of chemotherapy and radiotherapy on the gonads depends on the patient's age but may be high at all ages. The risk of a precocious menopause in over 39-year old women is substantial.[3] Research carried out in 1981 showed that about 50% of over 25-year old women who had been treated with MOPP developed precocious menopause within the following 5 years whereas only 20% of the under 25-year olds did so.[4]

The data regarding radiation-induced sterility vary widely. Temporary sterility can occur following a single fraction of 1.7-6.4 Gy to the ovaries; permanent sterility can result from a single fraction of 3.2-10 Gy.[5]

For years, we have been trying to reduce gonadal damage to improve the psychological status of these patients, not only affected by neoplasia but also informed that there might be a possibility of sterility. It is obligatory to suggest semen analysis and freezing to young male patients.[6,7] It is not, however, easy to carry out analogous procedures in female patients; on the other hand, hormone therapy administered during cytotoxic treatment, to prevent gonadal damage, has not produced the expected results.

Lateral or medial transposition of the ovaries prior to pelvic irradiation results in ovarian doses of 4-5% and 8-10% respectively. The screened ovaries receive the same dose of radiotherapy. The risk of ovarian failure increases with ovarian radiation dos-

es in excess of 5 Gy.[8] Ovariorrhexis has been used in the past with deluding results.[5] These data, together with the risk of extrauterine pregnancy, contraindicate such a method.

Recently oocyte freezing and ovarian tissue cryopreservation have been proposed to bypass the effects of iatrogenic damage to the ovary, but these procedures are still experimental. Nevertheless, during natural or iatrogenic menopause, the uterus preserves the capacity to respond to steroidal hormones and to permit implantation and development of an embryo obtained through oocyte donation and *in vitro* fertilization.

Oocyte donation, introduced in 1984 to treat premature ovarian failure, is an assisted reproductive technique that has an increasing number of indications, and has now become an accepted method of family building in many countries. The original indications for oocyte donation were premature menopause, genetic disease and inaccessible ovaries; with the passing of time, several other indications have been suggested, such as gonadal dysgenesis, postchemotherapy and radiation castration, recurrent abortion, maternal chromosomal abnormalities, and women in their forties, and post-menopausal patients in their fifties and recently even in their sixties.[9-12]

The pregnancy rate in these women is comparable to the group of patients from which the oocytes are harvested, generally aged less than 35 years, independently of the cause for which the oocyte donation was performed.[13] There is concern about the healthy status of women donating their gametes, and several recommendations have been suggested in order to avoid the transmission of infective diseases and genetically inherited diseases in the offspring.[14-19]

We describe 6 patients with previous Hodgkin's disease who safely carried a pregnancy to term. The pregnancy was achieved by oocyte donation and *in vitro* fertilization and intrauterine embryo transfer or oocyte intracytoplasmic insemination.

There are few papers reporting on women who underwent this procedure after therapy for Hodgkin's disease. Thus, we believe it may be useful to publish these data in order to give a message of hope to all women who have paid the price of precocious menopause in their struggle against their malignancy.

Design and Methods

The only ideal interval between the end of therapy for the Hodgkin's disease and a pregnancy could be one that respects both the clinical situation of the patient and satisfies the couple wishes. Nevertheless, we advise all patients to wait at least 24 months between the end of the therapy and an eventual pregnancy.

We retrospectively reviewed the series of data from 6 patients affected by Hodgkin's disease observed in our Institute between 1972 and 1991. At the time of diagnosis two patients were adolescent. The patients' characteristics are presented in Table 1.

All patients had been previously treated with chemotherapy regimens including alkylating drugs (procarbazine) and/or subdiaphragmatic radiotherapy (inverted Y) producing gonadal damage.

The first patient was 12 years old at diagnosis and had stage II A disease: she received four cycles of PROVECIP[20] chemotherapy and mantle radiotherapy; the second patient, 12 years old and staged III B, was treated with six cycles of MOPP, three cycles of ABVD and subdiaphragmatic radiotherapy. The third patient, 19 years old and staged IV B, received eight cycles of

Table 1. Patient characteristics: from diagnosis of the Hodgkin's disease to the last follow-up.

Pts (years)	*Age **	*Date of diagnosis*	*Stage*	*Chemo therapy*	*Radio therapy (Gy)*	*Hormone therapy (Kg)*	*Date of delivery Sex*	*Month of delivery*	*Weight of neonate*	*Gestosis*	*Cesarean section*	*Last follow-up °*
P.A.	12	03/72	IIA	4 Provecip	Mantle 20	NO	06/89 M F	8th	2.6-1.6	YES	YES	168th
F.E.	12	05/79	IIIB	6 MOPP+3 ABVD	Inverted Y 44	NO	02/96 M	8th	2.3	NO	YES	146th
F.L.	19	05/84	IVB	8 MOPP/ABVD	Inverted Y 20	YES	01/93 F	7th	1.3	YES	YES	90th
B.M.	22	04/89	IIIA	4 COPP/ABVD	Mantle + Inverted Y 30	YES	03/99 F	9th	2.5	NO	NO	104th
M.A.	30	03/91	IIIB	8 MOPP/ABVD	Mantle + Lumboaortic barr 20	NO	08/87 M F	7th	1.5-1.6	YES	YES	64th
L.L.	28	06/91	IIIB	8 OPP/ABVD	Mantle + Inverted Y 20	YES	11/98 M	9th	3.8	NO	YES	72nd

**At diagnosis of Hodgkin's disease; ° Calculated from the end of therapy to the date of birth. Abbreviations: Pts= patients; M= male; F= female; Provecip= procarbazine + vinblastine + cyclophosphamide + prednisone; MOPP= mechloretamine + vincristine + procarbazine + prednisone; ABVD= adriamycin + bleomycin + vinblastine + dacarbazine; COPP= cyclophosphamide + vincristine + procarbazine + prednisone; OPP= vincristine + procarbazine + prednisone.*

alternated MOPP/ABVD chemotherapy followed by subdiaphragmatic and mantle radiotherapy; the fourth patient, 22 years old and staged III A, was treated with four cycles of alternated COPP/ABVD plus mantle and subdiaphragmatic radiotherapy. The fifth patient, aged 30 and staged IIIB, received eight cycles of ABVD/MOPP chemotherapy followed by mantle and subdiaphragmatic radiotherapy. Therefore, 5/6 patients received subdiaphragmatic radiotherapy (one patient lumboaortic bar and four patients inverted Y) and all patients achieved complete remission. Mantle irradiation includes: all supradiaphragmatic lymph nodes (mediastinal, hilar, axillary, lateral cervical and supraclavicular lymph nodes); lumboaortic bar includes: lumboaortic lymph nodes; inverted Y includes: all subdiaphragmatic lymph nodes (lumboaortic, iliac and inguinal lymph nodes), splenic hilum and the spleen. The uterus is not included in the irradiation field and the ovaries are screened.

During treatment, 3/6 females had hormone therapy in an attempt to prevent gonadal damage. They suffered from hypergonadotropic amenorrhea (FSH>50 mL/U, LH >40 mL/U) as a result of chemotherapy and radiotherapy.

Eggs were donated in a private setting after written informed consent by patients undergoing oocyte donation, *in vitro* fertilization and intrauterine embryo transfer or an oocyte intracytoplasmic insemination program for tubal disorders or because of severe infertility factors in the male partner. The donors' age ranged between 24 and 36 years, they all tested negative for HIV, hepatitis B and C, Herpes virus, cytomegalovirus, syphilis and toxoplasmosis. Genetic screening was negative for cystic fibrosis, thalassemia A and B, GSPD deficiency and the karyotype was normal.

Controlled ovarian hyperstimulation was achieved using a long protocol of GnRH agonist and FSH administration (Metrodin HP 75, Serono, Italy) at a dosage tailored to the individual patient's response. HCG 10,000 IU (Profasi, Serono, Italy) was given to induce follicular maturation when a consistent rise in plasma estradiol was identified associated with 3 or more follicles sized ≥ 17 mm in diameter. Administration of HCG was timed to enable oocyte recovery to be scheduled 35 hours after HCG injection. Oocyte recovery was performed by transvaginal ultrasound guided follicular aspiration. Oocyte donation, *in vitro* fertilization and intrauterine embryo transfer or oocyte intracytoplasmic insemination procedures were performed as previously described.

All recipient women were pre-treated with estradiol valerate at a dosage of 4-6 mg/day for at least 10 days, synchronized with the donor's cycle. Progesterone administration 50 mg im/day was added 3 days before embryo transfer. A beta-HCG test was performed 14 days after embryo transfer and progesterone was increased to 200 mg/day in patients who tested positive.

Results

The six women received 16 attempts of egg donation. Two patients became pregnant after the first attempt, 2 after the second, 1 after the third and 1 after the fourth for an overall pregnancy success rate of 100% and a cycle success rate of 37%. A total of 64 oocytes were used for fertilization by the husbands' semen. The fertilization rate was 75%, the cleavage rate was 95%, the number of embryos transferred per patient was 2.5±0.4 (range 2-4). The implantation rate was 17%.

Patients delivered 72-168 months (median 97) after the end of their therapy for Hodgkin's disease.

Both patients treated in adolescent age had premature menopause; in one patient the premature delivery was associated with gestosis. Two women developed pre-eclampsia during the third trimester of pregnancy and had a Cesarean section; one patient gave birth to a female weighing 1,350 g; the second patient delivered by Cesarean section twin children (a male weighing 1,500 g and a female weighing 1,600 g). The other two patients carried their pregnancy safely to term: one gave birth to a female (2,500 g), the other a male (3,800 g).

There were no major birth defects in the children. All these children are, to date, healthy and well; their median age is 4 years (range 1-11 years).

The observations of premature delivery, gestosis and low birth weight, variably present in all patients, reflect the negative effect of therapies on uterus. Data concerning uterine size before the reproductive program are not available because of the difficult interpretation of this parameter in women with iatrogenic hypoestrogenism.

The negative effect on the uterus seems to be correlated with the age of patients; in fact, women treated in adolescence seem to have more substantial uterine damage than women treated in adult age.

Discussion

This study confirms the possibility of women treated for Hodgkin's disease having full-term pregnancies with the help of steroidal therapy and oocyte donation and shows that careful clinical and obstetric surveillance allows post-chemotherapy sterility to be overcome. As widely recognized, egg donation can be the solution to fertility problems in patients with premature ovarian failure. In particular the possibility of

having children has become an important goal in patients with hematologic neoplasias, a long expectation of life and a chance of total recovery. Although some alternative methods have been suggested, such as oocyte freezing and ovarian tissue cryopreservation, to date these procedures are still under investigation and they have not been utilized in women with cancer to preserve their future fertility. Furthermore, in the case of cryopreserved tissue there is concern about the possibility of reintroducing cancer cells into the patient from whom the tissue was taken before starting chemotherapy. However, egg donation remains the only treatment in women with iatrogenic premature ovarian failure. This procedure is not allowed in all countries because it is governed by different laws in the different nations.[21,22]

Greater attention to these problems would be advisable, considering the legislative aspects in our country and the possibility of safeguarding fertility in these patients. Taking care of this delicate matter would be a positive signal for patients who can achieve recovery.

In summary, focusing attention on long-term survivors, we have set a goal: to improve their quality of life, psychophysical well-being as a whole, and not merely health, must be considered.

In our experience of the follow-up of 200 children born from parents affected by Hodgkin's disease, these children do not appear to have negative signs in the psycho-intellectual sphere. Only one child was affected by autism. These data are also confirmed by other studies reported in the literature.[23]

Nevertheless, it is very important to follow these children for a long period in order to evaluate the long-term effects of chemotherapy to their parents on physical growth, intellectual and neurologic functions, gonadal function, reproduction capacity, and transplacental carcinogenesis.

Contributions and Acknowledgments

APA and CA were responsible for the conception of the study, direct supervision, revision of the final version, recruitment and day-to-day contact with participants.

EC, MS, DF and RME contributed to the execution of the study, wrote the paper and contributed to the interpretation of data.

The order of authorship was established on the basis of the role of each author in the context of the study.

Funding

Supported in part by CNR 95.02109.CT., Italy.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Paolo G. Gobbi, who acted as an Associate Editor. The final decision to accept this paper was taken jointly by Dr. Gobbi and the Editors. Manuscript received January 15, 2001; accepted May 3, 2001.

Potential implications for clinical practice

Focusing attention on precocious menopause in women treated for Hodgkin's disease would give a message of hope confirming the possibility of these women having a full-term pregnancy with the help of appropriate therapy and oocyte donation.

References

1. Schover LR, Rybicki LA, Martin AB, Bringelsen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. Cancer 1999; 86:697-709.
2. Anselmo AP, Cartoni C, Bellantuono P, Maurizi-Enrici R, Aboulkair N, Ermini M. Risk of infertility in patients with Hodgkin's disease treated with ABVD vs MOPP vs ABVD/MOPP. Haematologica 1990; 75:155-8.
3. Ermini M, D'Autilia MT, Mammarella G, et al. Aspetti endocrini della post-menopausa iatrogena: indagine retrospettiva in pazienti trattate con radio e/o chemioterapia per linfomi Hodgkin e non Hodgkin. LXII Congresso della Società Italiana di Ginecologia e Ostetricia; 1983 Sept 21-24; Bologna, Italy. Monduzzi Editore.
4. Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, De Vita VT. Long-term follow up of ovarian function in woman treated with MOPP chemotherapy for Hodgkin's disease. Am J Med 1981; 71:552-6.
5. Morra E, Lazzarino M, Inverardi D. Il rischio di infertilità nella terapia della malattia di Hodgkin. Progressi in Ematologia Clinica 1985; 4:251-66.
6. Redman JR, Bajorunas DR, Goldstein MC, et al. Semen cryopreservation and artificial insemination for Hodgkin's disease. J Clin Oncol 1987; 5:233-8.
7. Scammel GE, White N, Stredonska J, Henry WF, Edmonds DK, Jeffcoate SL. Cryopreservation of semen in men with testicular tumour or Hodgkin's disease: results of artificial insemination of their partners. Lancet 1985; 2:31-2.
8. Madsen BL, Giudice L, Donaldson SS. Radiation-induced premature menopause: a misconception. Int J Radiat Oncol Biol Phys 1995, 32:1461-4.
9. Anselmo AP, Cavalieri E, Maurizi Enrici RM, et al. Hodgkin's disease during pregnancy: diagnostic and therapeutic management. Fetal Diagn Ther 1999; 14:102-5.
10. Fenichel P, Letur-Kornirsch H, Martin-Pont B, Mathieu C, Thepot F. Results of oocyte donation in France. (Study Group on Oocyte Donation). Contracept Fertil Sex 1999; 6:457-9.
11. Thepot F, Julliard JC. 1998 French results on medically assisted reproduction with gamete cryopreservation and donation. French Federation of CECOS. Contracept Fertil Sex 1999; 27:452-6.
12. Ahuja KK, Simons EG, Edwards RG. Money, morals and

medical risks: conflicting notions underlying the recruitment of egg donors. Hum Reprod 1999; 14:279-84.
13. Westergaard HB, Johansen AM, Erb K, Andersen AN. Danish National IVF Registry 1994 and 1995. Treatment, pregnancy outcome and complications during pregnancy. Acta Obstet Gynecol Scand 2000; 79:384-9.
14. Witz CA, Duan Y, Burns WN, Atherton SS, Schenken RS. Is there a risk of cytomegalovirus transmission during in vitro fertilization with donated oocytes? Fertil Steril 1999; 71:302-7.
15. Shulman A, Frenkel Y, Dor J, Levran D, Shiff E, Maschiach S. The best donor. Hum Reprod 1999; 14:2493-6.
16. Tucker MJ, Morton PC, Wright G, Sweitzer CL, Massey JB. Clinical application of human egg cryopreservation. Hum Reprod 1998; 13:3156-9.
17. Shulman A, Frenkel Y, Dor J, Levran D, Hendler I, Mashiach S. The outcome of in-vitro fertilization treatment by egg donation and intracytoplasmatic sperm injection for severe male factor infertility: a preliminary report. Hum Reprod 1998; 13:2158-60.
18. Spandorfer SD, Moomjy M, Davis OK, Barmat LI, Cholst I, Rosenwaks Z. Oocyte donation: does a previous attempt affect a subsequent attempt? Fertil Steril 1998; 70:222-6.
19. Jobanputra K, Toner JP, Denoncourt R, Gibbons WE. Crinone 8% (90 mg) given once daily for progesterone replacement therapy in donor egg cycles. Fertil Steril 1999; 72:980-4.
20. Mandelli F, Biagini C, Baroni CD, et al. Treatment of non Hodgkin's lymphoma with "PROVECIP" (procarbazine, vinblastine, cyclophosphamide and prednisone). Haematologica 1980; 65:107-18.
21. Barlyn S. Compensating egg donors. Is the money worth it? N J Med 1999; 96:33-5.
22. Lewis V, Saller DN Jr, Kouides RW, Garza J. Survey of genetic screening for oocyte donors. Fertil Steril 1999; 71:278-81.
23. Janov AJ, Anderson J, Cella DF, et al. Pregnancy outcome in survivors of advanced Hodgkin's disease. Cancer 1992; 70:688-92.