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LETTER TO THE EDITOR

Spontaneous conception after autologous hematopoietic stem cell transplantation: a case report

Charlotte Dupont[1,2], Cécile Bally[3], Florence Eustache[1], Nathalie Sermondade[1,2], Brigitte Benzacken[1], Pierre Fenaux[3] and Rachel Lévy[1,2]

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Dear Editor,

Allogeneic or autologous hematopoietic stem cell transplantation (HSCT) allows many patients with hematological malignancies to obtain prolonged survival and often disease cure. Autologous HSCT is particularly effective in acute promyelocytic leukemia (APL), a subtype of acute myeloid leukemia (AML) after relapse with conventional treatment. However, iatrogenic endocrine disturbances and reproductive failure are frequently-encountered late effects, which have a major impact on the quality of life.[1] Conditioning regimens with total body irradiation (TBI) and intensive chemotherapy before autologous or allogeneic HSCT are known to cause permanent infertility, a risk that can be prevented by sperm banking.[2]

While few cases of successful conception or spermatogenic recovery after HSCT, with chemotherapy alone, or combined with TBI conditioning, have been reported[1,3–12] (**Table 1**), other studies assessing male fertility after HSCT have not reported any conception, highlighting the increased risk of altered reproductive function after HSCT.[1,13]

In 2002, a 20-year-old man was diagnosed with APL. He was treated with daunorubicin 60 mg m^{-2} once daily for three consecutive days (total dose 180 mg m^{-2}) and all-trans retinoic acid (ATRA) 45 mg m^{-2} until complete remission. Consolidation was performed with two cycles of daunorubicin using 60 mg m^{-2} once daily from day 1 to day 3, and 45 mg m^{-2} from day 1 to day 3. Continuous 6-mercaptopurine 90 mg m^{-2} once daily and methotrexate 15 mg m^{-2} once weekly, combined with intermittent ATRA 45 mg m^{-2} once daily for 15 days every 3 months were used for maintenance. The patient relapsed in January 2004, and was retreated with arsenic trioxide (10 mg day^{-1} for a month), ATRA (80 mg day^{-1} for 2 days and 40 mg day^{-1} for 2 days) and idarubicin (IDA) (20 mg). A subsequent cycle of treatment was performed 1 month later with arsenic trioxide (10 mg day^{-1}, 5 days $week^{-1}$ for 5 weeks) and IDA (20 mg day^{-1} twice). Since no sperm banking could be performed before the first chemotherapy, semen cryopreservation was planned 3 months after discontinuation of chemotherapy in September 2004. Not surprisingly, a zero sperm count was observed. After a semen cryopreservation attempt, the patient was given cytarabine (3800 g twice a day for 5 days) and IDA (20 mg day^{-1} twice). In October 2004, he received a conditioning regimen for autograft, combining busulfan (BU) 1 mg kg^{-1} per 6 h (70 mg×4 day^{-1}) for 4 days and cyclophosphamide (CY) (60 mg kg^{-1} day^{-1}) for 2 days. Altogether, the patient whose body surface area was 2 m^2, received 900 mg daunorubicin, 100 mg IDA, 45.6 g cytarabine, 1120 mg BU, 8400 mg CY, 570 mg arsenic trioxide associated with ATRA, methotrexate and mercaptopurine.

Considering the diagnosis of azoospermia, his wife stopped contraception in 2005. In January 2008, she spontaneously conceived and delivered a healthy boy in October 2008.

In 2010, the patient was still in complete remission. Because of the fear of relapse, sperm cryopreservation was planned. Semen parameters were assessed in August 2010 according to WHO classification: the volume was 4.3 ml, the concentration 127×10^6 ml^{-1} with 46% vitality and 30% motility (20% rapid linear progression and 10% slow progression). Sperm morphology using the David criteria showed 29% normal forms. Sperm DNA fragmentation was assessed by the TUNEL assay (*In Situ* Cell Death Detection Kit, Fluorescein; Roche Applied Science, Meylan, France), which found an increase in the DNA fragmentation rate reaching 30%. Fluorescence *in situ* hybridization was performed and no sperm aneuploidy was noted for chromosomes 13, 21, X and Y. In January 2012, the couple conceived a second child. The pregnancy is still ongoing.

This case report emphasizes the possibility for men to restart spermatogenesis after HSCT conditioning and to spontaneously conceive healthy children, even after repeated azoospermia diagnosis. Repeated sperm controls are needed, even many years after HSCT. Indeed, the time-to-pregnancy between HSCT and conception has often increased in the case reports (**Table 1**). It is also of importance to inform a couple who do not plan to conceive children that the observed azoospermia may be transient, and the use of contraceptive methods should, when indicated, be envisaged. Very few cases of spermatogenic recovery after HSCT for APL have been published: for the first time, the status of the nucleus was available. Despite moderate sperm DNA fragmentation, no chromosome anomaly was observed and the patient's healthy child does not suffer from any congenital abnormalities. Indeed, both cancer and high doses of radiation and chemotherapeutic agents have been associated with genomic instability, suggesting a possible transmission of DNA damage to the offspring through sperm cells.[14] Nevertheless, contradictory results concerning sperm DNA damage

[1]AP-HP, Jean Verdier hospital, reproductive biology unit-CECOS, Paris 13 University, Bondy 93140, France; [2]Paris 13 University, Nutritional epidemiology unit (UREN, UMR U557 Inserm, U1125 Inra, Cnam, CRNH IdF) Bobigny 93017, France and [3]AP-HP, Avicenne hospital, Hematology unit, Paris 13 University, Bobigny 93000, France
Correspondence: Dr C Dupont (charlotte.dupont@jvr.aphp.fr)
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Table 1 Some published case reports of successful conception and/or spermatogenesis recovery after HSCT

	N	*Diagnosis*	*Age (year)*	*HSCT*	*Chemotherapy conditioning*	*TBI*	*Delay (month)*	*Sperm count (million per ml)*	*Conception*	
Facon, 1993[4]	1	CML	25	ALLO	CY	YES	33	NA	Spontaneous	Proven paternity
Pakkala, 1994[7]	1	CML	28	ALLO	DAU, CY	YES	48	0	Spontaneous	Proven paternity
Shepherd, 1996[9]	1	APL	33	AUTO	BU, MEL, CY	NO	72	1	Spontaneous	Proven paternity
Sanders, 1996[8]	35	AA (28), ALL (1), AML (2), CML (2), LYMPH (2)	10.9–41.7	NA	CY (*n*=28), BU+CY (*n*=2), CY+TBI (*n*=5)	YES: *n*=5	NA	NA	YES	
Jacob, 1998[6]	1	AA	NA	ALLO	CY	NO	67	69	NA	
Jacob, 1998[6]	1	AML	NA	ALLO	CY	YES	75	13	NA	
Jacob, 1998[6]	1	AML	NA	AUTO	CY, ADRIA, BCNU, 6TG, ARA-C	NO	68	67	NA	
Jacob, 1998[6]	1	AML	NA	AUTO	CY, ADRIA, BCNU, 6TG, ARA-C	NO	50	32	NA	
Jacob, 1998[6]	1	CGL	28	ALLO	CY	YES	72	NA	Spontaneous	
Jacob, 1998[6]	1	AML	NA	AUTO	CY, DOXO	NO	NA	NA	Spontaneous	
Check, 2000[3]	1	AML	25	AUTO	BU, CY	NO	60	30.8/12.5	Spontaneous (ovarian stimulation)	
Petti, 2003[10]	1	ALL	20	AUTO	CY	YES	168	OAT	ICSI	
Rovo, 2006[12]	1	AA	NA	ALLO	CY	NO	72	Normal	Spontaneous	
Rovo, 2006[12]	1	AA	NA	ALLO	CY	NO	108	Normal	Spontaneous	
Rovo, 2006[12]	1	AML	NA	ALLO	CY, ETO	YES	108	Normal	Spontaneous	
Ignatov, 2010[5]	1	CML	33	ALLO	DEC, DAU	YES	54	0	ICSI-TESE	
Ignatov, 2010[5]	1	Hodgkin	17	AUTO	CBV, MOPP/AV	NO	192	0	ICSI-TESE	
Borgmann-Staudt, 2012[11]	2	NA	NA	ALLO	NA	NO	NA	NA	Spontaneous	

Abbreviations: AA, aplastic anemia; ADRIA, adriamycin; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; ALLO, allogeneic HSCT; APL, acute promyelocytic leukemia; ARA-C, cytosine arabinoside; AUTO, autologous HSCT; BCNU, bis-chloroethyl nitrosourea; BU, busulphan; CBV, CY+BCNU+VP16 (etoposid); CGL, chronic granulocytic leukemia; CML, chronic myeloid leukemia; CY, cyclophosphamide; DAU, daunorubicin; DEC, decitabine; DOXO, doxorubicin; ETO, etoposide; ICSI, intracytoplasmic sperm injection; ICSI-TESE, ICSI with testicular sperm extraction; LYMPH, lymphoma; MEL, melphalan; MOPP/AV, mechlorethamine+vincristine+procarbazine+prednisone/adriamycin+vinblastin; OAT, oligo-astheno-teratozoospermia; 6TG, 6-thioguanine.

in cancer survivors have been published; an increased aneuploidy evaluated 6 months after treatment, reverted to pre-treatment values after a few years.[15] Most of the studies conducted on offspring of cancer survivors failed to show any increased incidence of congenital abnormalities.[16] Further investigations and more case reports are needed to assess the effect of HSCT on sperm chromosomes.

AUTHOR CONTRIBUTIONS

CD, CB, PF and RL cared for the patient and collected clinical information. NS, FE, BB performed the laboratory tests. CD, NS drafted the manuscript, which was revised by FE, PF and RL. NS, BB took part in critical discussion.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interest.

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