Acceptability and feasibility of post-treatment fertility preservation in women previously treated for hematological diseases

Fertility preservation (FP) is a critical component of medical care for children, adolescents and young adults with hematological diseases undergoing gonadotoxic therapy, given the high survival rates associated with these conditions. In women, the risk of premature ovarian insufficiency (POI) depends on the type and dose of treatment, as well as the age at diagnosis and the initial ovarian reserve (OR). Fertility preservation is most efficient when done prior to treatment (32% and 33% live birth rate after oocyte and ovarian tissue cryopreservation respectively)[1] but it is not always feasible because of disease-related factors (e.g., need for urgent treatment, severe thrombocytopenia or neutropenia, risk of malignant contamination) or patient-related factors (poor clinical status, cultural prohibitions) and lack of knowledge, particularly in the early 2000s.[2] Consequently, it is still possible to encounter women in consultation who did not benefit from FP prior to treatment. In such cases, the possibility of performing FP post-treatment should be considered.

Few studies have reported their experience with FP post-treatment, and none have specifically evaluated the feasibility of FP based on prior treatments received.[3-6] Importantly, data that may guide clinicians on when post-treatment FP is feasible, when it can reasonably be forgone, and when referral should ideally occur remain scarce. The aim of our single-center retrospective study was to assess ovarian function and the feasibility of oocyte cryopreservation in women already treated for a malignant or non-malignant hematological disease.

In this study, women included between 2013 and 2021, were referred by their hematologist, for the first time, to the fertility preservation consultation localized inside the hematology consultation department, irrespective of any desire for childbearing. Information regarding hematological diagnosis, reason for no anterior FP, treatment history, and post-treatment ovarian function was reviewed from their medical records. Patients were categorized into three groups (G1, G2 and G3) based on their prior treatments: G1 included women who had undergone hematopoietic stem cell transplantation (HSCT), G2 comprised those treated with chemotherapy containing bifunctional alkylating agents (BFAA) without HSCT and G3, women treated with no BFAA (*Online Supplementary Table S1*). OR was assessed using antral follicular count (AFC) via transvaginal ultrasound and blood hormone assays, including follicle-stimulating hormone (FSH; IU/L) and anti-Müllerian hormone (AMH; ng/mL). Women presenting with amenorrhea lasting more than 4 months and an FSH level >25 UI/L were classified as having POI. Women still menstruating were categorized as having diminished OR (DOR; AMH <1.2 ng/mL) or normal OR (NOR; AMH >1.2 ng/mL).[7] Based on the treatment received, OR, pregnancy occurrence, and the feasibility of a FP through oocyte vitrification (OV) following controlled ovarian stimulation (COS), were analyzed for each group. Differences between treatment groups were assessed using Mann-Whitney test for continuous variables and Fisher's exact tests for categorical data. Kaplan-Meier survival analysis estimated cumulative pregnancy rates, with univariate cox models comparing groups. A significance threshold of $P<0.05$ was applied throughout. All statistical analyses were conducted using STATA-18 software (StataCorp LLC, College Station, TX, USA). Ethics approval was granted by the Cochin University Hospital Ethical Review Committee for publications, Paris, France (reference AAA-2023-09016).

Fifty-eight consecutive women were included in this study (G1: N=19, G2: N=32 and G3: N=7), 51 women (87.9%) had malignant hematological conditions, while seven (12.1%) had severe non-malignant diseases (*Online Supplementary Table S2*). The median age at treatment and FP consultation was 23.5 years (range, 1.0-41.0) and 28.9 years (range, 17.6-42.6) respectively and was not different between the three groups (Table 1). However, G1 patients experienced a significantly longer interval between treatment completion and their first FP consultation ($P<0.001$). Post-treatment ovarian function assessment was available for 48 women (82.7%). In G1, OR was significantly impaired compared to G2+G3 ($P\leq0.001$), consequently, the risk of POI was significantly higher in G1 compared to G2+G3 ($P<0.001$). Age at treatment in G1 was statistically higher in women with POI than in those with DOR ($P=0.02$). When comparing G2 and G3, no significant differences were found in hormonal parameters, except for a significantly lower AFC in G2 ($P=0.03$). Two women in G2 were diagnosed with POI, while none in G3. The median cumulative dose of cyclophosphamide received in G2 was 2,926 mg/m^2 (range, 1,000-7,200) (Table 1).

Twenty-one women expressed a desire to have a child following treatment. Thirteen women became pregnant, ten through natural conception, one through assisted reproductive technology (ART) and two through oocyte donation. Ten live births were achieved (Table 1). Natural pregnancies (NP) occurred in nine women in G2 (9/32) and one in G3 (1/7), median age at pregnancy was 30.8 years (range, 27.5-36.7). Three women in G2 experienced a second NP (*Online Supplementary Table S2*). The cumulative rate of NP in the overall population reached 35% by 7.5 years post-treatment

Table 1. Characteristics of women at post-treatment fertility preservation consultation according to the type of treatment received.

Variables	General population	G1	G2	G3	*P* (G1/G2+G3)	*P* (G2/G3)
N (%)	58 (100.0)	19 (32.7)	32(55.2)	7 (12.1)	-	-
Median age at TTT, years (range)	23.5 (1.0-41.0)	21.0 (1.0-36.6)	23.0 (5-41)	29.0 (14.0-33.2)	0.308	0.323
Median age at HSCT, years (range)	-	25.8 (2.7-37.4)	NA	NA	-	-
Allo-HSCT, N (%)	15 (25.8)	15 (78.9)	0	0	-	-
MAC/RIC regimen; N (%)	9 (15.5)/6 (10.3)	9 (60.0)/6 (40.0)	-	-	-	-
Auto-HSCT, N (%)	4(6.9)	4 (21.1)	0	0	-	-
Total cyclophosphamide dose, mg/m^2 (range)	NA	NA	2,926 (1,000-7,200)	0	-	-
Malignant hematological diseases, N (%) B-ALL T-ALL AML CML HL NHL	51 (87.9) 11 (19.0) 7 (12.1) 9 (15.5) 1 (1.7) 16 (27.6) 7 (12.1)	12 (63.2) 2 (10.5) 1 (5.3) 4 (15.8) 1 (5.3) 1 (5.3) 3 (21.0)	32 (100.0) 9 (28.1) 6 (18.8) 0 0 13 (40.6) 4 (12.5)	7 (100.0) 0 0 5 (71.4) 0 2 (28.6) 0	- - - - - - -	- - - - - - -
Non-malignant hematological diseases, N (%) Bone marrow failure Sickle cell disease Fanconi anemia	7 (12.1) 2 (3.4) 2 (3.4) 3 (5.2)	7 (36.8) 2 (10.5) 2 (10.5) 3 (15.8)	- 0 0 0	- 0 0 0	- - - -	- - - -
Median age at FP consultation, years (range)	28.9 (17.6-42.6)	29.8 (17.5-40.9)	27.7 (17.9-42.6)	29.9 (17.7-35.1)	0.502	0.797
Median time from TTT to FP consultation, years (range)	3.2 (0.2-24.8)	5.9 (0.8-24.8)	2.0 (0.15-16.3)	1.6 (0.6-3.4)	<0.001	0.534
OR, N (%) Median age at OR evaluation, year (range) Median time from TTT to OR evaluation, years (range) Median hormonal levels FSH, UI/L (range) AMH, ng/mL (range)	48 (82.7) 28.3 (14.6-41.2) 3.3 (0.3-24.8) 9.6 (3.3-160.8) 0.50 (0.01-13.20)	16 (84.2) 28.2 (15.4-41.2) 5.9 (1.0-24.8) 42.5 (4.8-160.8) 0.07 (0.01-1.00)	27 (84.4) 27.9 (18.7-38.9) 1.9 (0.3-7.5) 7.8 (3.3-98.5) 1.00 (0.05-7.13)	5 (71.4) 28.2 (14.6-32.9) 1.4 (0.3-2.8) 6.7 (3.5-11.8) 2.50 (0.11-13.20)	- 0.831 <0.001 <0.01 <0.001	- 0.925 0.327 0.132 0.259
Antral follicular count, N (%) Median follicle number, N (range)	39 (67.2) 7 (0-40)	11 (57.9) 4 (0-7)	24 (75) 9 (1-25)	4 (57.1) 20 (11-40)	- <0.001	- 0.03
Ovarian status N (%) NOR DOR POI	 13 (27.1) 24 (50.0) 11 (22.9)	 0 7 (43.8) 9 (56.2)	 10 (37.0) 15 (55.6) 2 (7.4)	 3 (60.0) 2 (40.0) 0	 - - <0.001	 - - 0.737
Childbearing desire, N (%)	21(36.2)	9 (47.4)	9 (28.1)	3 (42.8)	-	-
Total pregnancy, N Natural pregnancy, N (%=N/total population) Lives birth Elective abortion Ectopic pregnancy	13 10 (17.2) 10 2 1	1* 0 1 - -	9+1* 9 (28.1) 7 2 1	1+1# 1 (14.3) 2 - -	- - - - -	- - - - -

Continued on following page.

*Oocyte donation; #assisted reproductive technology. AMH: anti-Müllerian hormone; AML: acute myeloblastic leukemia; B-ALL: B-cell acute lymphoblastic leukemia; CML: chronic myeloid leukemia; DOR: diminished ovarian reserve; FP: fertility preservation, FSH: follicle-stimulating hormone; G1: group 1 included women who had undergone hematopoietic stem cell transplantation (HSCT); G2: group 2 comprised women treated with chemotherapy with bifunctional alkylating agents without HSCT; G3: group 3 women treated with chemotherapy with no bifunctional alkylating agents; HL: Hodgkin lymphoma; HSCT: hematopoietic stem cell transplantation; LH: luteinizing hormone; MAC: myeloablative conditioning regimen; NA: not applicable; NHL: non-Hodgkin lymphoma; NOR: normal ovarian reserve; OR: ovarian reserve; POI: premature ovarian insufficiency; RIC: reduced-intensity conditioning regimen; T-ALL: T-cell acute lymphoblastic leukemia; TTT: treatment.

(Figure 1A). In G2 and G3, this rate reached or exceeded 60% at 7.5 years, whereas G1 showed a significantly lower cumulative rate of 10% (Figure 1B) (P<0.05). Women with lymphoma, who received cumulative cyclophosphamide doses up to 7,200 mg/m², showed the highest pregnancy rates, while those with non-malignant conditions had the lowest (Figure 1C). Among the 21 women (36.2%) who had expressed a desire to have children, eight (38.1%) got pregnant. Among the five other pregnant women (13.5%) who did not wish to have children, two underwent elective abortions. FP was considered for 30 women (62.5%) who had an OR deemed suitable for COS. Eleven women (36.7%) proceeded with the procedure, while 19 (63.3%) declined the offer. FP was performed in two of six, six of 19 and three of five women in G1, G2 and G3, respectively. The median age at OV was 24.5 (range, 19.3-34.3). In G2, the cumulative dose of cyclophosphamide received was 2,500 mg/m² (range, 1,000-6,700). The median number of vitrified oocytes was six (range, 0-20). G1 patients exhibited a notably low number of retrieved oocytes (N=2), while G2-G3 patients demonstrated broader variability, with two to 20 vitrified oocytes per women (Table 2).

To our knowledge, this study represents the largest series evaluating NP and the feasibility of FP post-treatment in women with hematological diseases, based on individualized treatment history. In our overall cohort, 17.2% of women achieved a NP, which is lower than the 38% reported by Chow *et al.*[8] However, when considering only women who had expressed a child desire, 38.1% achieved a NP.

By stratifying our study population into three treatment

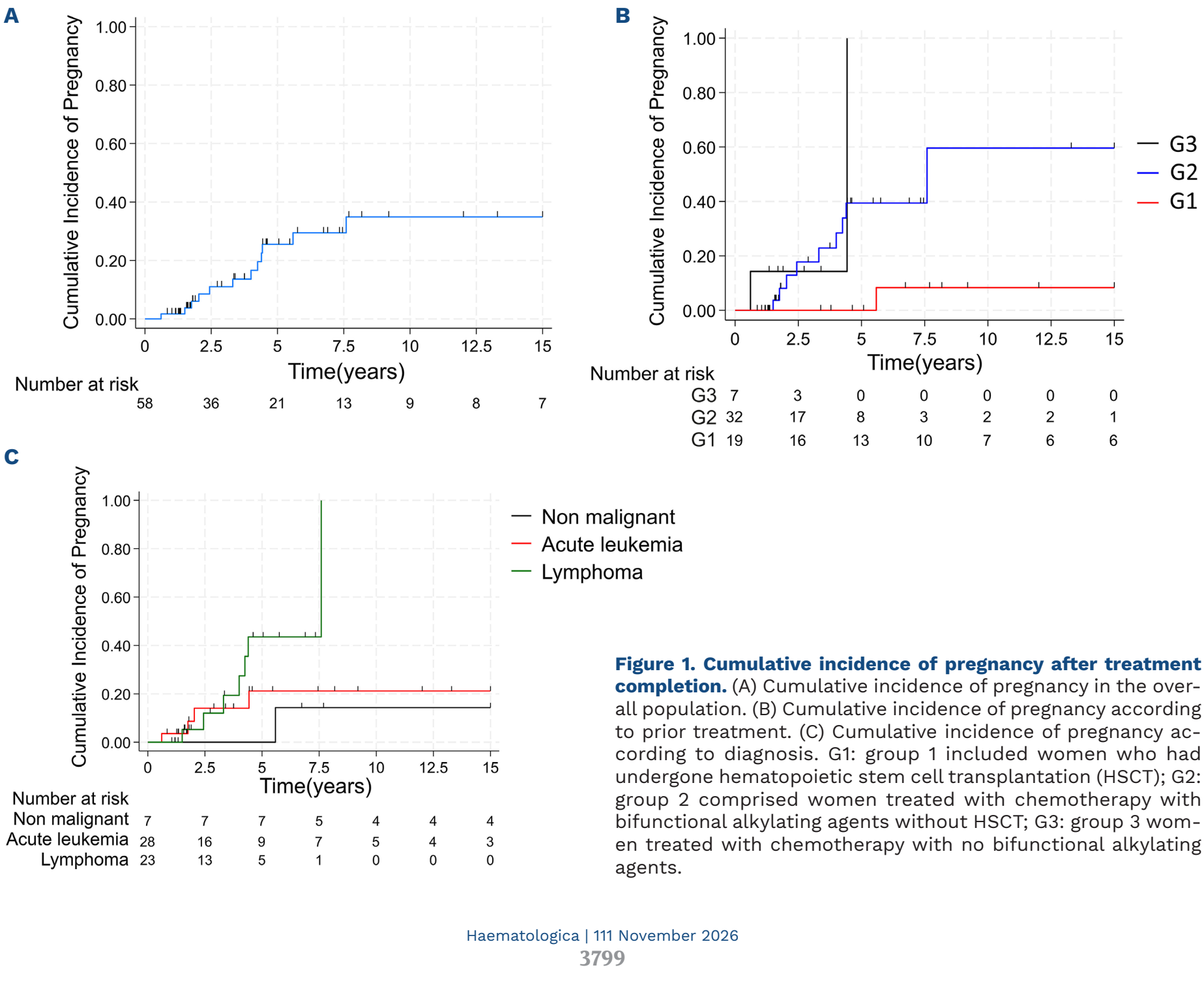


Figure 1. Cumulative incidence of pregnancy after treatment completion. (A) Cumulative incidence of pregnancy in the overall population. (B) Cumulative incidence of pregnancy according to prior treatment. (C) Cumulative incidence of pregnancy according to diagnosis. G1: group 1 included women who had undergone hematopoietic stem cell transplantation (HSCT); G2: group 2 comprised women treated with chemotherapy with bifunctional alkylating agents without HSCT; G3: group 3 women treated with chemotherapy with no bifunctional alkylating agents.

Table 2. Characteristics of women undergoing fertility preservation post treatment and results of fertility preservation.

Hematological disease	TTT group	Age at TTT, years	Time since the end of TTT, years	CP dose, mg/m^2	Age at COS, years	FSH, UI/L	LH, UI/L	E2, pmol/L	AMH, ng/mL	AFC	N of COS cycles	Cumulative N of vitrified oocytes
Median (range)	-	16.0 (4.0-29.2)	7.7 (1.6-14.3)	2,500 (1,000-6,700)	24.5 (19.3-34.3)	6.8 (3.3-18.2)	5.2 (1.8-31.1)	146.8 (25.0-651.0)	1.1 (0.1-5.0)	11 (4-28)	1 (1-3)	6 (0-20)
Fanconi A	G1	6.0	14.3	1,000	20.4	6.8	4.2	94	1.0	7	1	2
CML	G1	4.0	12.8	6,700	19.5	4.8	8.2	462	0.1	4	1	0
B-ALL	G2	16.0	1.6	1,000	21.1	9.7	5.6	147	1.8	11	1	3
B-ALL	G2	15.9	8.3	1,000	27.1	12.9	5.2	169	0.3	9	2	10
B-ALL	G2	15.6	7.2	1,000	23.6	6.8	5.4	106	1.3	21	1	6
T-ALL	G2	15.0	2.1	4,000	19.3	18.2	31.1	651	1.1	4	1	4
T-ALL	G2	19.0	8.4	5,250	29.7	7.4	4.4	121	1.0	11	3	18
NHL	G2	26.4	7.7	4,500	34.3	3.3	1.8	497	1.7	11	1	9
AML	G3	22.3	2.0	0	24.5	11.8	3.6	25	5.0	28	1	20
AML	G3	29.0	4.0	0	33.4	3.6	3.9	25	4.4	7	1	2
HL	G3	29.2	2.7	0	32.3	6.8	5.6	172	0.9	11	2	6

AFC: antral follicular count; AMH: anti-Müllerian hormone; AML: acute myeloblastic leukemia; B-ALL: B-acute lymphoblastic leukemia-B; CML: chronic myeloid leukemia; COS: controlled ovarian stimulation; CP: cyclophosphamide; E2: Estradiol; Fanconi A: Fanconi anemia; FSH: follicle-stimulating hormone; G1: group 1 included women who had undergone hematopoietic stem cell transplantation (HSCT); G2: group 2 comprised women treated with chemotherapy with bifunctional alkylating agents without HSCT; G3: group 3 women treated with chemotherapy with no bifunctional alkylating agents; HL: Hodgkin lymphoma; LH: luteinizing hormone; NHL: non-Hodgkin lymphoma; T-ALL: T-acute lymphoblastic leukemia; TTT: treatment.

groups, we may provide practical guidance for clinicians regarding which patients may benefit from post-treatment FP. As expected, women in G1 exhibited the lowest probability of NP[9] and the poorest response to COS, underscoring the critical importance of performing FP prior to treatment whenever possible. Nevertheless, this should be qualified by a recent study by Sockel *et al.*, reporting a 3.4% pregnancy rate after HSCT, with 72% natural conceptions. Consistent with their findings, we also confirmed that age at treatment is a determinant of ovarian reserve.[10] In G2, AMH levels and prior exposure to high dose of cyclophosphamide did not appear to correlate with the likelihood of natural pregnancy before 30 years old, as previously reported.[8,11] Six women in G2 with altered OR became pregnant, and three of them experienced a second natural pregnancy. This observation aligns with the findings of Chow *et al.*, who reported no correlation between cumulative cyclophosphamide dose, up to 11 g/m^2, and pregnancy outcome.[8] In G3, hormonal profiles were close to normal, consistent with the findings of van den Berg *et al.*[12]

Few studies have reported on COS in women after cancer treatment, either during ART protocols for embryo or OV.[6,13,14] The median oocyte yield number in our cohort was comparative to a recent study[6] and reflects our choice to proceed with COS despite DOR, due to the fertility preservation context. Importantly, no difference was observed in the number of retrieved oocytes between G2 and G3. These results suggest that post-treatment FP should not be dismissed in women treated with BFAA without HSCT, even in the presence of DOR and that repeated COS cycles may be discussed to optimize oocyte yield,[4,6,15] as implemented in three women within our cohort.

Recently, Miquel *et al.* reported a promising cumulative live birth rate of 38% from oocytes collected after cancer treatment,[5] highlighting the value of post-treatment FP. However, even when FP was offered, many women chose not to undergo the procedure, as previously reported by Benedict *et al.*[16]

From a practical standpoint, ovarian function assessment and counseling should be systematically proposed within 1-2 years after completion of chemotherapy.[15] Women treated with HSCT are poor candidates for post-treatment FP. These women should be counselled accordingly and referred, whenever possible, for FP before HSCT. In contrast, women treated with BFAA without HSCT have a lower risk of compromised fertility and a potential for NP and successful oocyte retrieval, highlighting that fertility potential may persist despite altered OR. They should then receive individualized counselling regarding reproductive options, regardless of the hormonal profile. Contraceptive advice should also be provided when there is no desire for pregnancy (cf. 2 elective abortions in our series). Women treated with non-alkylating agents are suitable candidates for post-treatment FP, or annual monitoring of ovarian function for those considering delaying FP.

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https://doi.org/10.3324/haematol.2025.300093

Received: October 23, 2025.
Accepted: March 18, 2026.
Early view: April 2, 2026.

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Disclosures

No conflicts of interest to disclose.

Contributions

CC, NB, and CP contributed to the design and the data analysis. All authors contributed to the interpretation of the analysis results. CC, NB, and CP wrote the original draft of the letter and incorporated the comments by the co-authors in all subsequent drafts. All authors provided review and edits and approved the final draft of the letter.

Acknowledgments

Thanks goes to the technicians who performed the oocyte vitrification process.

Data-sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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