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Original Article

Ovarian protection and fertility preservation in women with cancer: A French national registry analysis between 2005 and 2014

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ABSTRACT

Objective: Ovarian failure is a common effect of treatment for cancer. The aim of this study was to describe the practices concerning ovarian protection and fertility preservation in young women treated for cancer.
Study design: Women between 15 and 49 years old diagnosed with cancer between 2005 and 2014 were studied, abstracted from a representative French National Healthcare database. To assess practices concerning ovarian protection, gonadotropin-releasing hormone (GnRH) agonist consumption and ovarian transposition were analyzed. For fertility preservation, GnRH agonist consumption, ovarian cryopreservation and oocyte cryopreservation were analyzed. Explanatory variables were analyzed using a multilevel model.
Results: A total of 2447 women were identified. Among the 553 patients exposed to ovarian failure, 74 (13%) had ovarian protection (67 received GnRH agonists, 7 underwent ovarian transposition). Among the 227 women exposed to fertility alteration, 53 (23%) had fertility preservation (37 received GnRH agonists, 16 had ovarian or oocyte cryopreservation). Factors associated with ovarian protection were age under 40 years old (OR = 1.56 [1.5–1.62], p = 0.006) and diagnosis of breast cancer (OR = 1.15 [1.08–1.22], p < 0.001). The only factor associated with fertility preservation was breast cancer (OR = 1.17 [1.1–1.24], p < 0.001). The five-year probability of pregnancy was 3.8% and 9.8% (p = 0.26) for women with and without fertility preservation, respectively.
Conclusion: Over the last decade, ovarian protection and fertility preservation concerned 13% and 23%, respectively, of young French women treated for cancer. Awareness about ovarian protection and fertility preservation remain insufficient and need to be extended to improve this major aspect of cancer management.

Introduction

Common effects of cytotoxic treatment for cancer are both global ovarian function alteration with menopausal symptoms, osteoporosis and decreased cardio vascular protection, and fertility alteration. Increasing survival rates in patients affected by oncological disease and advances in reproductive medicine have led to the development and increasing use of various ovarian function protection and fertility preservation techniques.

Different techniques and treatments are used to protect ovaries and preserve fertility for young women being treated for cancer. In breast cancer, a randomized study showed that the administration of a GnRH agonist with chemotherapy appears to protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility [1].

In patients receiving pelvic radiotherapy or brachytherapy, surgical ovarian transposition protects endocrine ovarian reserve [2].

According to the French recommendations, any child or patient of childbearing age receiving treatment with a potentially deleterious ovarian effect should be informed of this risk and of the benefits of an ovarian preservation. She will be referred to a specialist competent in reproduction preservation fertility [2].

The Echantillon Généraliste de Bénéficiaires (EGB) database is a permanent representative sample of the population protected by French health insurance, established in 2003 and allowing for the analysis of individual consumption of care [3].

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The aim of this study was to describe the practices about ovarian protection and fertility preservation in young women with cancer in France for the last 10 years and the determining factors.

Methods

Study population

The study population was women between 15 and 49 years old who were diagnosed with cancer from January 2005 to December 2014. We used the national database, EGB, to identify the study population. This national database is a representative sample of 1/97th of the French population covered by health insurance and was established in 2003. Access to the database was allowed after a three-day mandatory training. This panel is managed by the CNAMTS (National Health Insurance Fund for Social Workers) and was the subject of an agreement of the National Commission for Informatics and Liberties (CNIL). From the EGB, we obtained cancer declaration, type of cancer, and socio-demographic characteristics of patients, such as age, care department, health care coverage, and date of death. Medicalisation Program Information System (PMSI) databases, available from January 2005 to December 2014, were used to identify cancer treatments (surgery, radiation, and chemotherapy) and type of institutions. Procedures carried out for ovarian protection and fertility preservation (Ovarian transposition, ovarian cryopreservation, and oocyte cryopreservation) and GnRH agonist delivery were extracted from drugs consumption databases.

To estimate and to analyze practices concerning ovarian protection, we focused on women between 15 and 49 years old who had a possible ovarian alteration because of cancer treatment. Women without expected ovarian alteration (no chemotherapy or pelvic radiation) or with definitive ovarian alteration (bilateral ovariectomy) were excluded because they were not supposed to receive ovarian protection. Thus, to study ovarian protection, we included women who were 49 years old or less, who had chemotherapy and/or pelvic radiation.

Concerning the analysis of the women who were candidates for fertility preservation, we considered the subgroup of women between 15 and 40 years old who had a possible fertility alteration because of cancer treatment. Women with no expected fertility alteration (no chemotherapy or pelvic radiation) and those with definitive fertility alteration (bilateral ovariectomy and/or hysterectomy) were excluded because they were not supposed to receive fertility preservation. Thus, to study fertility preservation, we included women 40 years old or less who had chemotherapy and/or pelvic radiation.

Main outcomes

The main outcomes were as follows:

- For the ovarian protection analysis, GnRH agonist consumption and/or ovarian transposition within the first 6 months after cancer diagnosis.
- For fertility preservation, GnRH agonist consumption, ovarian cryopreservation or oocyte cryopreservation within the first 6 months after cancer diagnosis.

Secondary outcome

The secondary outcome studied was the cumulative incidence of pregnancies during the study for women between 15 and 40 years old candidates for fertility preservation.

Statistical analysis

The primary analysis used Fisher's test or chi square test according to the validity conditions to compare the ovarian protection and no ovarian protection women and the fertility preservation and no fertility preservation women.

A multilevel model with random intercept in univariate and multivariate analyses was performed to identify determining factors. The first level was the individual level, and the second was institutional.

The cumulative incidence of pregnancies was calculated via a Kaplan–Meier analysis. To identify prognostic variables of pregnancy, we used a Cox regression.

An alpha level of 0.05 was used to indicate significance.

Results

In the EGB database, we identified 2447 women between 15 and 49 years old with cancer from January 2005 to December 2014. A total of 1836 women had no expected ovarian alteration due to cancer treatment, and 58 had a definitive ovarian alteration because of bilateral ovariectomy. The 553 remaining patients with possible ovarian alteration related to cancer treatment were selected for the analysis of the use of ovarian protection methods (Fig. 1).

Among these women, 320 were excluded as candidates for fertility preservation because of age greater than 40 years old, and 6 were excluded because they had had a hysterectomy. The remaining 227 patients with possible fertility alteration related to cancer treatment were selected to analyze fertility preservation practices (Fig. 1).

Among the 553 women between 15 and 49 years old with possible ovarian alteration, 74 (13%) had ovarian protection: 67 received GnRH agonists, and 7 had ovarian transposition.

Among the 227 women between 15 and 40 years old with possible fertility alteration, 53 (23%) had fertility preservation: 37 women received GnRH agonists, and 16 had ovarian or oocyte cryopreservation (Fig. 1).

Characteristics of candidates for ovarian protection and fertility preservation are presented in Table 1

For candidates of ovarian protection, the mean age was 40.1 (38.5–41.2) years old, 40.5% were treated for breast cancer, 96.7% received chemotherapy and 76.5% were treated in public institutions.

For candidates of fertility preservation, the mean age was 32.6 (30.8–34.5) years old, 43.2% were treated for breast cancer, 95.6% received chemotherapy and 80.6% were treated in public institutions.

Factors associated with ovarian protection and fertility preservation

In multilevel analysis, age under 40 years (1.56 [1.5–1.62], $p = 0.006$) and treatment for breast cancer (1.15 [1.08–1.22], $p < 0.001$) were significantly associated with ovarian protection (Table 2).

In multivariate multilevel analysis, type of cancer (breast cancer) was the only factor associated with fertility preservation (1.17 [1.1–1.24], $p < 0.001$) (Table 3).

Cumulative incidence of pregnancies

The five-year probability of pregnancy was 8.4% for women candidates for fertility preservation (Fig. 2).

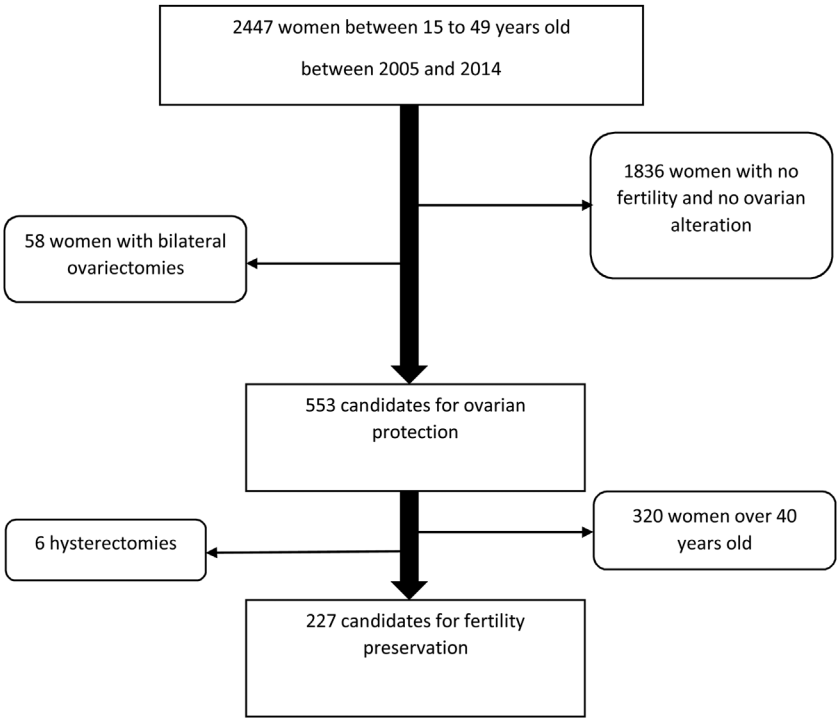

Fig. 1. Flow chart.

In univariate and multivariate analyses, the only factor associated with the probability of pregnancy was women's age at cancer diagnosis. Women over the age of 35 were significantly less likely to become pregnant (0.27 [0.09-0.82], p = 0.02) (Table 4).

Discussion

In this retrospective study evaluating fertility preservation and ovarian protection, using the French health care insurance registry between 2005 and 2014, only 23% and 13% of candidates underwent such management, respectively. Age younger than 40 years old and breast cancer were associated with a higher rate of ovarian protection. Breast cancer was the only factor influencing the use of fertility preservation.

Despite increasing data concerning the possibility of fertility and ovarian preservation [4,5] the rate has remained stable over the last decade. Beyond prospective randomized control trials and international recommendations, studies interesting in fertility preservation practices are based on surveys [6–8] and do not allow for a reliable analysis and estimation of real practices. This is the first national study providing the real use of ovarian and fertility preservation in cancer treatment of young women.

Worldwide, almost 1 million new cases of cancer occurred among young adults aged 20–39 years in 2012. The most common cancer types affecting women aged 20–39 years were breast

Table 1
characteristics of the 553 candidates for ovarian protection and the 227 candidates for fertility preservation.

	Candidates for ovarian protection N = 553	Candidates for fertility preservation N = 227
Age, years (mean, CI 95)	40.1 (38.5 – 41.2)	32.6 (30.8 – 34.5)
Universal healthcare coverage	123 (22%)	58 (25.2%)
Type of cancer		
Breast cancer	224 (40.5%)	98 (43.2%)
Digestive cancer	59 (10.7%)	16 (7%)
Gynaecologic pelvic cancer	67 (12.1%)	25 (11%)
Other	183 (33%)	88 (38.8%)
Radiation		
No	290 (52.4%)	125 (55%)
No pelvic radiation	201 (36.3%)	81 (35.7%)
Pelvic radiation	62 (11.2%)	21 (9.3%)
Chemotherapy		
Yes	535 (96.7%)	217 (95.6%)
Type of institution		
Public hospital	423 (76.5%)	183 (80.6%)
Private institution	62 (11.2%)	23 (10.1%)
NA	68 (12.2%)	21 (9.3%)
Year of treatment		
Before 2009	290 (52.4%)	116 (51.1%)

Data are expressed as n (%) unless otherwise specified.
CI: Confidence interval.

Table 2
Factors associated with ovarian protection (Univariate and multivariate multilevel analysis).

	Univariate OR [95% IC]	p	Multivariate OR [95% IC]	p
Age < 40	1.08 [1.02 – 1.14]	0.007	1.56 [1.5 – 1.62]	0.006
Universal healthcare coverage	0.91 [0.81–1.11]	0.33		
Type of cancer				
Others	1			
Breast	1.16 [1.09–1.23]	<0.001	1.15 [1.08–1.22]	<0.001
Digestive	1.0 [0.9–1.1]	0.9	1.01 [0 .91–1.11]	0.9
Gynecological	1.05 [0.09–2.02]	0.3	1.05 [0.96–1.15]	0.3
Radiation				
pelvis	0.98 [0.88–1.08]	0.7		
chemotherapy	0.95 [0.81–1.09]	0.45		
Health institutions				
Public	1	0.03	1	0.1
Private	1.1 [1.02–1.2]		1.07 [0.98–1.16]	
Before 2009	1.06 [0.99–1.11]	0.07	1.05 [0.99–1.11]	0.09

CI: Confidence interval.

Table 3
Factors associated with fertility preservation (Univariate and multivariate multilevel analysis).

	Univariate OR [95% IC]	p	Multivariate OR [95% IC]	p
Age < 35	1.04 [0.92–1.16]	0.5		
Universal healthcare coverage	0.85 [0.72–0.98]	0.01	0.98 [0.91–1.05]	0.6
Type of cancer				
Others	1		1	
Breast	1.26 [1.14–1.39]	<0.001	1.17 [1.1–1.24]	<0.001
Digestive	1.16 [0.93–1.38]	0.2	1.01 [0.91–1.11]	0.9
Gynecological	0.97 [0.78–1.16]	0.75	1.06 [0.96–1.16]	0.3
Radiation				
Pelvic radiation (gynecologic or other pelvic cancers)	0.99 [0.78–1.2]	0.96		
Chemotherapy	1.11 [0.81–1.41]	0.5		
Health institutions				
public	1	0.4		
private	1.09 [0.9–1.27]			
Before 2009	1.05 [0.94–1.17]	0.4		

CI: Confidence interval.

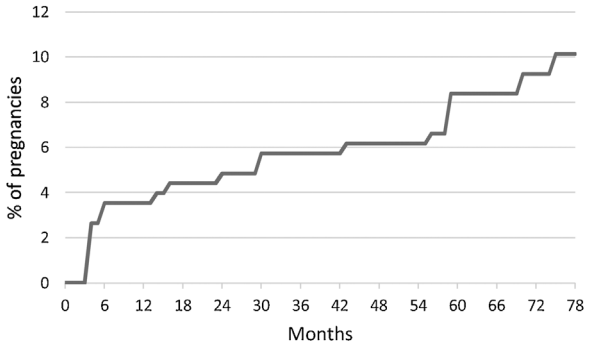

Fig. 2. Cumulative incidence of pregnancies among women with possible fertility alteration.

cancer (30%), cervical cancer (18%), and thyroid cancer (10%) [9]. With advances in cancer treatment and improved survival rates, issues such as loss of fertility are coming to the forefront. Retrospective studies indicate that 30%–40% of reproductive-age survivors experience a feeling of loss of control over their reproductive future and are discontented with their current number of children [10]. In a survey of more than 600 young women with early-stage breast cancer, 29% reported that concern about infertility influenced their treatment decisions [6]. Hence, the American Society of Reproductive Medicine (ASRM) and the American Society of Clinical Oncology (ASCO) have put forth official guidelines recommending that patients be educated about the effect of cancer treatment on fertility and fertility preservation options [11,12]. The European Society of Gynecological Oncology (ESGO) decided in 2007 to launch the Task Force for Fertility Preservation in Gynecologic Cancer. This task force was developed to promote knowledge of infertility induced by treatment of gynecologic cancers among healthcare workers and the public through national and international collaboration among oncologists, reproductive specialists [13].

Strategies for fertility preservation prior to chemotherapy depend on the time required, the woman's age, its risks and efficacy, and the individual preference of the patient [14]. In the present study, the analysis of the preservation of fertility was based on the cryopreservation of embryos and oocytes, which are the two established methods of fertility preservation. In October 2012, ASRM published an official guideline stating that mature oocyte cryopreservation should no longer be considered experimental and can be recommended with appropriate counseling to patients receiving gonadotoxic therapies for cancer [15]. In our database, no oocyte cryopreservation was found for fertility preservation before 2011. Administration of GnRH agonists with chemotherapy is suggested to protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility [1]. In our study, GnRH analogues were frequently used. Indeed, 67 women with possible ovarian and 37 women with possible fertility alteration received analogues.

Pelvic or whole-abdomen radiation > 6 Gy in adult women induced a high risk of amenorrhea and ovarian failure [16]. Specific techniques for preventing radiation damage to the ovaries are used, such as ovarian transposition, in addition to embryo and

Table 4
Factors associated with pregnancies (Univariate and multivariate Cox regression).

	Univariate HR [95% IC]	p	Multivariate HR [95% IC]	p
Age > 35	0.25 [0.09–0.68]	0.007	0.27 [0.09–0.82]	0.02
Universal healthcare coverage	1.64 [0.66–4.07]	0.3		
Type of cancer				
Breast	0.42 [0.17–1.08]	0.07	0.57 [0.31–3.2]	0.1
Gynecological	0.6 [0.13–2.7]	0.5	0.65 [0.11–3.01]	0.5
Radiation				
Pelvic radiation	0.59 [0.08–4.59]	0.6		
Chemotherapy	0.89 [0.12–6.7]	0.9		
Health institutions				
private	1.12 [0.32–3.86]	0.9		
Before 2009	0.54 [0.20–1.45]	0.2		
Fertility preservation	0.41 [0.19–1.15]	0.1	0.52 [0.20–1.17]	0.1

HR: Hazard Ratio.
CI: Confidence interval.

oocyte cryopreservation, with good results in protection of ovarian function [17–19]. In our study, ovarian transposition was a procedure used for ovarian protection in 7 women with possible ovarian alteration.

In the management of young women with cancer, loss of fertility remains an under-represented topic. A retrospective survey of 1041 California women diagnosed with cancer, aged 18–40, found that only 61% were counseled by their oncologists about the risk of infertility, and only 5% were referred to reproductive endocrinologists [8]. This finding is in accordance with the results of the present study, since in the 227 women with possible fertility alteration, 16 had ovarian or oocyte cryopreservation (7%), which is classically performed by reproductive endocrinologists.

Studies have shown significant discrepancies in referrals based on ethnicity, parity, and cancer type. Women with breast cancer were more likely to have fertility preservation [20], which is concordant with our results. Breast cancer is treated by gynecologists who are probably more aware of the problem of preservation of fertility and have easier access to these techniques. Moreover, referring women of childbearing age to a reproductive endocrinologist was more likely among female physicians [21]. Letourneau et al. observed that women who are childless, younger than 35 years old, Caucasian and with a higher socio-economic level may be more likely to be counseled about the risks of cancer treatment to fertility or to preserve fertility [8]. We also investigated the impact of the Universal Healthcare Coverage allocated under an income threshold giving entitlement, an indicator of socio-economic status, and we found that it was associated with a less frequent use of fertility preservation, which is consistent with Letourneau et al. [8].

Using a sample of a national database reporting different ovarian protection and fertility preservation techniques, the present study allows for an evaluation of the real practices. Furthermore, we are interested in the rate of pregnancy after cancer treatment. The five-years cumulative incidence of pregnancy was 8.4%. The pregnancy rate found was generally low but was concordant with the study of Hulsbosch et al., reporting real-life experience in centers for fertility preservation; only 32% of patients in remission (18% of all patients) attempted to become pregnant, with a pregnancy rate of 55%, mostly after spontaneous conception [22]. The pregnancy rate among the 159 women in the study of Hulsbosch et al. receiving fertility preservation was only 10%. In our registry, no information about cancer prognosis and remission was available, making the interpretation of the pregnancy rates difficult. The only factor associated with probability of pregnancy was women's age at cancer diagnosis. Indeed, being older than 35 years decreased the probability of pregnancy by 83%.

Our study has several limitations. The EGB was only a sample of the French population. This sample was representative, but the number of women included was limited, as was the number of ovarian protection and fertility preservation procedures, and the number of pregnancies. We had no information concerning the type of chemotherapy potentially impairing ovarian function. However, it is well known that most chemotherapeutic agents are gonadotoxic, particularly those with alkylating agents, such as cyclophosphamide and ifosfamide, posing the highest risk of ovarian failure [16].

In conclusion, over the last decade, ovarian function protection and fertility preservation concerned 13% and 23%, respectively, of French women treated for cancer, mainly for breast cancer.

Considering these rates and previous international surveys, an unmet need remains for reproductive health counseling and fertility preservation in young age women diagnosed with cancer. Awareness and information about ovarian protection and fertility preservation are still insufficient and need to be extended to improve this major aspect of cancer management. In France, the National Institute of Cancer's 2014–2019 plan aims to ensure access to the preservation of fertility by systematizing the information of the patients concerned, as soon as the therapeutic proposal is announced, about the risks of cancer treatments for their subsequent fertility and about the current possibilities of preserving fertility i. by developing new professional recommendations on the assessment of the risks of impaired fertility, the possibilities of preserving fertility before the start of treatments, and the techniques of preserving fertility according to sex, age, pathology and treatments at multidisciplinary consultation meetings, and ii. by ensuring equal access of patients to the territory of clinico-biological platforms for the preservation of fertility [23].

Declaration of Competing Interest

Authors had no Conflict of Interest.

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