



Fertility preservation in patients of childbearing age treated for breast cancer: A nationwide cohort study

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ABSTRACT

Background: Approximately 7% of breast cancers are diagnosed in women under 40. Question of subsequent fertility has become fundamental. We aimed to evaluate the rate of fertility preservation (FP) by oocyte retrieval (OR) after ovarian stimulation in patients of childbearing age, managed for breast cancer with adjuvant chemotherapy in France, reuse rate of frozen gametes and live births rate (LBR) after treatment.

Methods: We included 15,774 women between 18 and 40 years old, managed by surgery and adjuvant chemotherapy for breast cancer, between January 2011 and December 2020 from a French health registry. Patients with OR after breast surgery and before chemotherapy were considered as FP group; those with no OR as no FP group. To compare LBR with French population independently of age, we calculated Standardized Incidence Rates (SIR) of live births using indirect standardization method.

Results: FP rate increased gradually since 2011, reaching 17% in 2019. A decrease in use was observed in 2020 (13,9%). Among patients with at least 2 years of follow-up, gamete reuse rate was 5,6%. Births after cancer were mostly from spontaneous pregnancies. Among patients with at least 3 years of follow-up, LBR was 19,6% in FP group, 3,9% in second group. SIR of live births was of 1,05 (95% CI = 0.91–1.19) and 0.33 (95% CI = 0.30–0.36) in FP and no FP group respectively.

Conclusion: Oncofertility activity increased until 2019 in France, reaching 17%. Gamete reuse rate was low. Births resulted mainly from spontaneous pregnancies. SIR of live births was lower in no FP group.

1. Introduction

Approximately 10–15% of breast cancers are diagnosed in premenopausal women, 7% of which are in women under 40 (1,2). In France, this represents approximately 4000 new cases per year. Average age at diagnosis for women under 40 is 32.9 years [1,2]. A large majority have an indication for adjuvant chemotherapy followed by antihormone therapy for at least 5 years [3]. With the increase in age at first birth, many patients will not have children at the time of diagnosis. An epidemiological study of a large cohort of women treated for breast cancer showed that 25% of women under 40 years old with breast cancer were nulliparous, 20% had one child [4].

It is established that occurrence of pregnancy in patients treated for

breast cancer has no impact on either survival or risk of recurrence [5]. The question of subsequent fertility has become fundamental. Some studies reported particularly low pregnancy incidences after cancer: between 3% and 8% in women younger than 45 years [6,7]. Female infertility after treatment of breast cancer may be the consequence of 2 phenomena that often add up: gonadotoxicity of chemotherapy, which directly alters the stock of primordial follicles; and physiological ovarian aging, which causes follicular loss during the years of medical contraindication for pregnancy.

In France, since 2011 (Article L. 2141 11, amended by Law 2011–814 of July 7, 2011), law provides: “Any person whose medical care is likely to impair fertility, or whose fertility is likely to be prematurely impaired, may benefit from the collection and conservation of

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his or her gametes, for the purpose of medically assisted procreation, or to the preservation and restoration of his or her fertility” [8]. National Cancer Plan “2014–2019” integrated these recommendations about fertility preservation (FP) [9].

FP is a very evolving field from technical point of view. Authorized in France since 2011, oocyte vitrification enabled considerable development of oncofertility. It is the most widely used and recommended method for FP in case of breast cancer treatment [10,11]. Management of breast cancer is mainly based on the following scheme: surgery-vitrification-adjuvant chemotherapy.

Impact of FP legislation and Cancer Plan over the last decade has not been evaluated, particularly in the context of breast cancer. Evaluation of birth rates after breast cancer is particularly difficult because it requires long-term follow-up and multicentric studies. It is even more difficult to assess the rate of FP and re-use of frozen oocytes/embryos.

The primary objective of this study was to evaluate the rate of FP by oocyte vitrification in patients of childbearing age, managed for breast cancer with indication of adjuvant chemotherapy in France between 2011 and 2020. The secondary objectives were to evaluate the rates of reuse of frozen oocytes/embryos and live births after treatment.

2. Methods

This is a descriptive nation-wide cohort study, based on exhaustive claim data in France.

2.1. Population and settings

This study was conducted using French Hospital Claim Data, called Programme de Medicalisation des Systemes d'Information (PMSI). All inhabitants of France have a unique social security identifier throughout life and are represented in this database ($66,4 \times 10^6$ in 2016). All private and public hospitals data are registered within PMSI. Diagnoses, surgical acts and births are coded using International Classification of Diseases 10-th revision (ICD-10), French Classification Commune des Actes Médicaux (CCAM) and French Classification Groupes Homogènes de Malades (GHM) respectively. Codes used are summarized in Supplementary file 1.

Between January 2011 and December 2020, all patients between 18 and 40 years old who have undergone breast cancer surgery (CCAM: QEFA001 to QEFA013, QEFA015 to QEFA020 + ICD10 code C50) followed by adjuvant chemotherapy (ICD-10 code Z511 as primary diagnosis and ICD10 code C50 as secondary diagnosis in the same hospital stay, in the 6 months following surgery) were included. Surgery date was the inclusion date. Patients were not included if treatment started with chemotherapy (neo-adjuvant chemotherapy; ICD-10 code Z511 as primary diagnosis and ICD10 code C50 as secondary diagnosis in the same hospital stay, in the 3 months prior to surgery), or if they were pregnant at the time of surgery (live birth within 10 months following surgery, GHM code 14Z02, 14C02).

Using National Institute for Statistical and Economical Studies (INSEE) database, French population of women aged 20–39 years old included served as reference population for indirect standardization.

2.2. Data and outcomes

Our main outcome was the rate of FP. FP was defined by an OR (CCAM code JFFJ001) after breast surgery and before chemotherapy. To ensure a valid association between OR, adjuvant chemotherapy and breast cancer, we required a maximum of 3 months between breast surgery and OR, and 6 months between breast surgery and adjuvant chemotherapy. Patients who had OR were identified as FP group; those who didn't have OR as no FP group.

Our secondary aims were the embryo transfers (ET) (CCAM code JSED001) in the FP group and live births in FP and no FP group. Live birth after ET was defined as a live birth occurring within 10 months

after ET.

We collected age, dates of surgery/first chemotherapy/OR following surgery/ET/live births/death.

As this is a descriptive study, no other data were collected. Following data were not available in French Hospital Claim Data: medical history, parity, clinic-biological characteristics of breast cancer, ovarian assessment, results of OR (number of oocyte,.).

For standardization, we calculated the reference incidence rate using the number of live births observed in each age and each calendar year in France (Source: PMSI), and number of women in each 5-year age-class (Source: INSEE, National Federation of Regional Health Observatories (FNORS)).

2.3. Statistical analysis

Statistical analysis were done using SAS 9.4. Qualitative variables were described using numbers and percentages; quantitative variables using mean and standard deviation.

As patients frequently have hormonotherapy following adjuvant chemotherapy, pregnancy is frequently contraindicated during 2 years after surgery. We considered that patients were not supposed to start medically assisted procreation during this period: percentage of patients with ET was calculated in patients with at least 2 years of follow-up. Then, time required for conception and pregnancy duration is rarely shorter than 1 year. Therefore, percentage of patients with live birth was calculated in patients with at least 3 years of follow-up.

To consider different follow-up durations due to the end-of-study date (31-12-2020) or to death, the rate of first live birth following surgery was described using Kaplan-Meier curves, with date of surgery as date of start.

To compare live birth rates with French population independently of age, we calculated Standardized Incidence Rates (SIR) of live births using indirect standardization method. For each calendar year, we only included patients with at least 3 years of follow-up. Confidence Intervals (95% CI) were calculated for SIR(11).

For each analysis, results are given according to 4 age classes ([18–25 [, [25–30 [, [30–35 [, and [35–40]). We kept only 2 age classes for Kaplan-Meier curves for readability. Age classes for SIR calculation were based on available INSEE and FNORS classes.

2.4. Ethics

Ethics approval was obtained (IRB-MTP_2021_12_202101004).

3. Results

We identified 15,774 patients for analysis, between 18 and 40 years old, treated by surgery and adjuvant chemotherapy for breast cancer, between 2011 and 2020: rate of patients treated per year decreased during study period (1846 in 2011 vs 1206 in 2020). Among them, 381 (2,4%) had adjuvant chemotherapy more than 3 months after surgery; none of these patients had FP. During a mean follow-up of 5.2 years, 792 (5%) of patients died.

3.1. How many FP were performed ?

1650 patients (10,5%) had an OR in the 3 months following surgery and before chemotherapy: they were considered as the « FP group». Rates of FP are presented in Table 1, according to age and year of surgery. Age of patients who had FP remained stable over the years (data not shown). Rates of FP increased during the study period, reached a plateau between 16% and 17% from 2017. In 2020, the rate decreased: this mainly concerned patients between 25 and 35 years old.

At the end of the study period, more than 50% of patients under 30 years of age, 25% between 30 and 35 years old and 7% between 35 and 40 years old had a FP. Mean delay between surgery and first OR was of

Table 1
Percentage of patients with preservation of fertility, among patients treated for breast cancer with adjuvant chemotherapy, according to age group and year of surgery.

Date of surgery (year)	Patients treated for breast cancer with adjuvant chemotherapy									
	All patients		18–25 years old		25–30 years old		30–35 years old		35–40 years old	
	Total (N)	With FP N (%)	Total (N)	With FP N (%)	Total (N)	With FP N (%)	Total (N)	With FP N (%)	Total (N)	With FP N (%)
2011	1846	45 [2,4]	12	3 [25]	120	12 [10]	408	18 [4,4]	1306	12 (0,9)
2012	1793	70 [3,9]	17	2 [8,11]	110	14 [7,12]	388	33 [5,8]	1278	21 [1,6]
2013	1772	104 [5,9]	12	3 [25]	127	24 [9,18]	361	49 [6,13]	1272	28 [2,2]
2014	1707	134 [7,9]	14	4 [6,28]	105	30 [6,28]	398	70 [6,17]	1190	30 [2,5]
2015	1561	189 [1,12]	12	7 [3,58]	111	45 [5,40]	370	78 [1,21]	1068	59 [5,5]
2016	1524	221 [5,14]	17	9 [9,52]	102	55 [9,53]	361	83 [23]	1044	74 [1,7]
2017	1480	241 [3,16]	10	4 [40]	102	59 [8,57]	318	92 [9,28]	1050	86 [2,8]
2018	1472	247 [8,16]	14	9 [3,64]	85	42 [4,49]	359	115 [32]	1014	81 [8]
2019	1376	235 [1,17]	15	8 [3,53]	95	56 (59)	327	109 [3,33]	939	62 [6,6]
2020	1206	167 [9,13]	13	8 [5,61]	70	35 (50)	268	67 [25]	855	57 [6,7]

FP: Fertility preservation.

1.2 months (SD = 0.5), 95% of patients had only 1 OR.

3.2. What were fertility outcomes after FP (N = 1650) ?

Fig. 1 displays fertility outcomes of 1650 patients with FP and 14,124 without FP. Among patients with FP and at least 2 years of follow-up (N = 1243), 70 patients had at least one ET (5,6%); among them, 24 had several ET. First ET was performed on average 3.8 years after breast surgery (SD 1.7). Regarding age, 67 were over 30 years old.

Among the patients with FP, ET, and 3 years of follow-up (N = 69), just over half did not have a live birth (Fig. 1).

3.3. Fertility outcomes in the whole population with at least 3 years of follow-up (N = 11,429)

Among patients with at least 3 years of follow-up (N = 11,429 = 69 + 926+10,434), 606 (5.3%) had at least one live birth (Fig. 1). Chance of live birth was higher in patients with FP: in this group, chance of live

birth following spontaneous pregnancy was higher than following ET. In patients under 30 years old at the time of surgery, 25.4% had at least one live birth (data not shown).

Mean delay to first live birth was 4.5 years after surgery (SD 1.7). To take into consideration different follow-up durations, Kaplan-Meier curves of first live birth are displayed in Fig. 2.

To compare live birth rates to French population, Table 2 describes total number and Standardized Incidence Ratio (SIR) of live births. Comparatively to French population, SIR of live births was of 0.43 (95% CI = 0.40–0.46). In FP group, the SIR was of 1.05 (95% CI = 0.91–1.19), and in no FP group, it was of 0.33 (95% CI = 0.30–0.36).

3.4. Additional data

Among patient who did not have FP before chemotherapy (N = 14,124), 46 (0.3%) had recourse to medically assisted reproduction (ovarian stimulation and OR) after cancer treatment (minimum delay of 1.6 years after breast surgery, mean delay of 5.1 years).

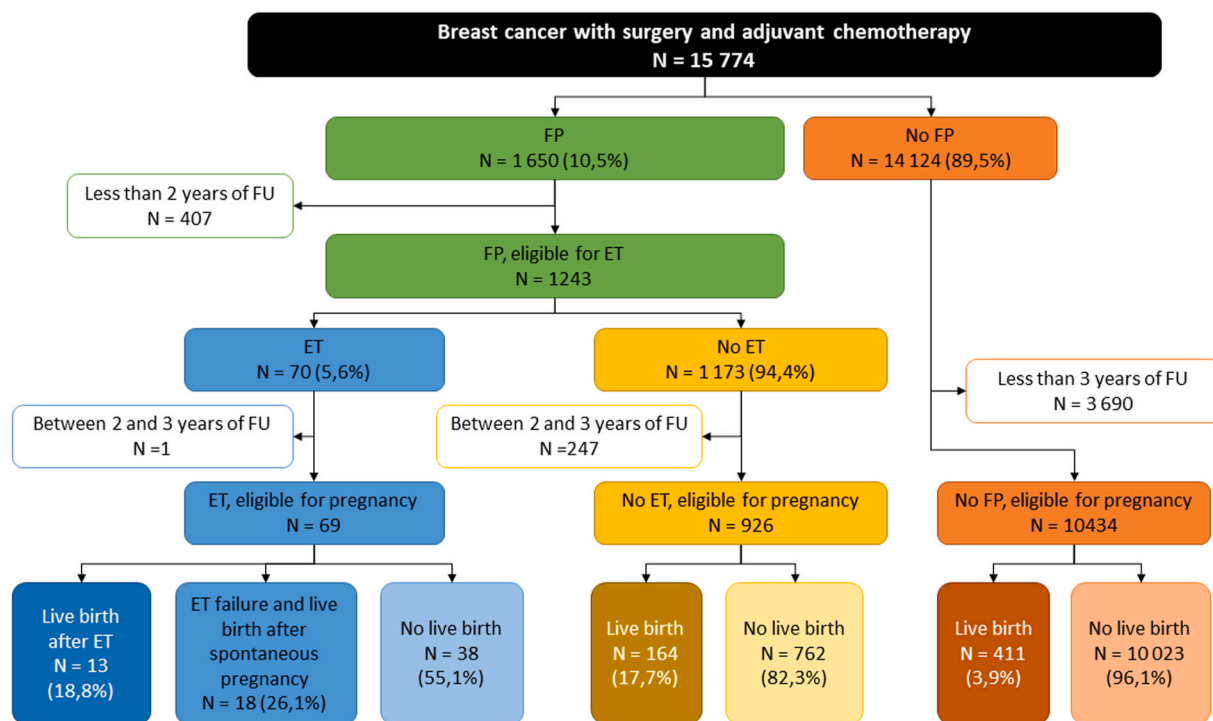
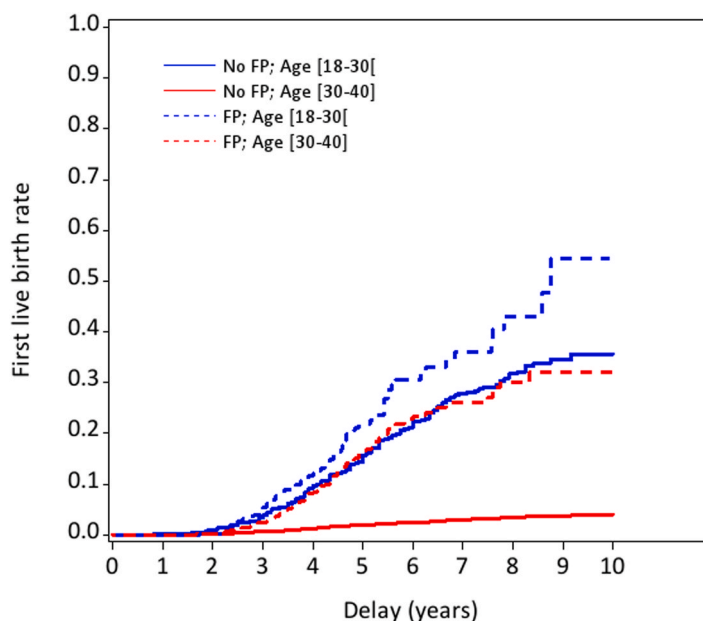


Fig. 1. Patients between 18 and 40 years old treated for breast cancer with adjuvant chemotherapy between 2011 and 2020 in France: fertility outcomes with and without fertility preservation (Number of patients with at least one live birth).

FP: fertility preservation; ET: Embryo Transfer; FU: follow-up.



Number of patients at risk	0	1	2	3	4	5	6	7	8	9	10
No FP; Age [18-30[744	699	634	562	480	396	306	227	144	70	0
No FP; Age [30-40]	13380	12337	11120	9792	8474	7133	5831	4392	2935	1497	0
FP; Age [18-30[429	386	321	258	180	107	59	36	17	5	0
FP; Age [30-40]	1221	1095	919	705	499	322	191	116	50	16	0

Fig. 2. Patients between 18 and 40 years old treated for breast cancer with adjuvant chemotherapy between 2011 and 2020 in France: Kaplan-Meier curves of first live birth among patients with and without fertility preservation and according to age group. In the y-axis: percentage of patients with at least one live birth; in the x-axis: delay to live births in year.

Table 2

Standardized Incidence Ratios of live births of patients treated for breast cancer with adjuvant chemotherapy between 2011 and 2020 and with at least 3 years of follow-up: Indirect standardization on French population incidence rates (includes total number of live births).

Live births		FP		No FP		All	
		N	SIR (95% IC)	N	SIR (95% IC)	N	SIR (95% IC)
Age group at surgery	All	214	1,05 (0,91–1,19)	437	0,33 (0,3–0,36)	651	0,43 (0,4–0,46)
	20–24	5	0,43 (0,14–0,88)	18	0,58 (0,34–0,87)	23	0,54 (0,34–0,78)
	25–29	72	0,9 (0,7–1,12)	149	0,55 (0,47–0,64)	221	0,63 (0,55–0,72)
	30–34	100	1,11 (0,9–1,34)	201	0,37 (0,32–0,42)	301	0,47 (0,42–0,53)
	35–39	37	1,66 (1,17–2,24)	69	0,15 (0,12–0,18)	106	0,22 (0,18–0,26)

FP: Fertility preservation; N: number of live births; 95% IC: 95% Confidence Intervals.

As mentioned before, among all, majority of patients had a live birth more than 3 years after surgery. Only 12 patients had a live birth before that time: 2 patients in FP group (spontaneous pregnancy) and 10 patients in no FP group (Fig. 2).

4. Discussion

In our study, number of patients who used FP increased progressively between 2011 and 2019, especially after the implementation of Cancer Plan In 2014. FP has mainly involved patients under 30 years old, with rates higher than 60% in some years. Rates are variable in the literature, ranging from 8.7% to 41%, all cancers combined [12] [–] [15]. As for breast cancer, Gosset et al. and Du Boulet et al. found a rate of 8.7% and 31% respectively [13]. This heterogeneity can be explained by the activity of each center and fertility techniques they proposed (in vitro maturation, cryopreservation of ovarian tissue, etc). Rate of recourse to FP was low considering that up to 59% of patients declared a desire for pregnancy at the time of their breast cancer diagnosis [16,17]. Several explanations can be put forward. Firstly, 92,4% and 69% of patients were over 30 and 35 years old respectively. These patients had potentially fulfilled their parental plans and did not wish to resort to FP. Secondly, despite reassuring data regarding FP and pregnancy after

breast cancer [14,18] [–] [21], oncofertility counseling is only proposed in 30–50% of cases by specialists [22]. Given reasons were: fear of delayed management of cancer and risk associated with ovarian stimulation in the context of hormone-dependent cancer [23,24]. Informing specialists remains a crucial issue [25]. Thirdly, some patients do not wish to undergo FP for the following reasons: emotional shock at diagnosis, fear of the impact of FP and pregnancy on cancer, inadequate information [16,17,26]. It has also been shown that question of subsequent fertility was of little concern at the time of diagnosis but became significant over time [27]. It therefore seems necessary to ask patients from the beginning of their care about their possible desire for pregnancy and to inform them in a clear and objective manner. Finally, it is also important to note that not all patients diagnosed with cancer at a young age desire biological child.

One of the main findings of this study is low reuse of gametes (5,6%). In literature, reuse rates varied from 3.6% to 18.7%, all cancers combined [12,14,28] [–] [31]. Robertson et al. found a higher reuse rate of 26.3% but also included preservations in the context of autoimmune disease [32]. Oktay et al. found a reuse rate of 25% [33]. Regarding time to reuse, Cobo et al. [28] and Oktay et al. [33] found a mean time of 4.1 and 5,2 years respectively. In our study, mean time was 3,8 years. Given that 35% of patients were preserved after 2016, we may have

underestimated the reuse rate. A longer follow up will be needed to have a complete assessment. Data on number of retrieved oocytes, obtained embryos and survival of thawing oocytes/embryos were not available in our database and could have impacted the reuse rate. However, according to literature, current techniques of FP seem to be efficacious [34, 35]. This study showed that approximately 1500 patients per year could have benefited from FP in France over the last decade. If we relate this result to incidence of breast cancer in France [36], it represented 2.5% of all breast cancers. Despite small proportion of patients and low reuse rate, question of FP is primordial and is source of additional stress when breast cancer is announced [16]. Regarding treatment management, 40% of patients reported that fertility had an impact on their treatment decision [16,17]. Access to oncofertility counseling and FP has been shown to improve quality of life [23].

In the literature, desire for pregnancy assessed at the time of diagnosis could vary from 24% to 80% [37] [–] [39]. In almost half of patients, desire for pregnancy no longer existed after treatment [38,39]. One of the reasons could be the “fear” of cancer recurrence in case of pregnancy, especially for hormone-sensitive tumors [16]. This could partly explain the birth rates in our study. Results are consistent with literature. A meta-analysis in young women treated with chemotherapy for breast cancer reported an incidence of pregnancy 40% lower in comparison with general population [40]. The study by Stensheim et al. on 27,556 survivors, including 1240 women treated between the ages of 16 and 45, showed a 67% lower chance of pregnancy in women treated for breast cancer compared with general population [4]. Another study from Scottish registries involved women up to 39 years at diagnosis (n = 23,201 including 10,271 nulliparous women) who were matched on age to women from the general population [41]. The incidence of spontaneous pregnancy was significantly lower for all cancers, with greater reductions after breast cancer. These low pregnancy rates after breast cancer can also be the consequence of the gonadotoxicity of the treatments used in this context, and of hormonal treatments which can delay the pregnancy project. Indeed, current recommendations favor a minimum of 2–3 years of hormone therapy before considering a therapeutic window for a pregnancy desire [33]. Antihormone therapy can also explain the mean delay before reuse of cryoconserved oocytes/embryos, which was over 3 years. An international study is underway to prospectively evaluate the feasibility and safety of discontinuing treatment after 18–30 months of hormone therapy in patients under 42 years of age [42]. The results of this study will provide additional data on the rate of gamete reuse, time to discontinuation of hormone therapy, risk of recurrence and pregnancy rate. If we compare FP and no FP group, the standardized incidence ratio of live births was higher in FP group, while the reuse of gametes and rate of pregnancies obtained through embryo transfer in this same group were low. FP alone cannot explain this higher incidence. One of the reasons could be the desire for pregnancy of FP group, which must have been greater at time of diagnosis and must have remained so after treatment. Another could be a better prognosis of response to ovarian stimulation in FP group, with reduced risk of primary ovarian insufficiency after treatment and higher chances of spontaneous pregnancy.

Number of patients managed with adjuvant chemotherapy has gradually decreased since 2011 (56 patients per year on average) and could be explained in particular by therapeutic de-escalation undertaken during the last decade [43,44]. It dropped more significantly in 2020. We also observed a decrease of FP in 2020 (17 vs 13.8%). One may wonder about the impact of global health crisis related to COVID-19. Rapid spread of Covid-19 epidemic has saturated the capacity of hospitals and health system [36]. Management of cancers has been greatly disrupted. Number of diagnoses has decreased significantly since the arrival of the epidemic, with a decrease of more than 50% in the number of mammograms performed between February and May 2020 (36). Number of breast cancer surgeries also decreased by 16% during the same period. However, FP would have remained available during this period [45]. Decrease of FP could be explained by the renunciation of

patients for fear of delayed oncological management due to COVID-19 infection. Further studies are needed to assess the impact of COVID-19 on oncological management and FP.

Regarding its descriptive aim, our study has the major advantage of being based on nationwide mandatory claim data base, and is therefore exhaustive and free from major selection bias. But this database is prone to measurement bias. In this study, we may have missed some ET, performed in private hospitals: we estimated that we missed around 10% of ET, which could not distort our results. We may have overestimated the number of patients with an efficient OR, because we did not know if oocytes were really vitrified. We also may have underestimated the number of live births: some patients could have moved out of the country or pursued pregnancy using a gestational carrier. Finally, we choose to report only live births as fertility outcome because miscarriages and ectopic pregnancies are often treated in outpatient departments, and are therefore not all recorded. This may have led to an underestimation of fertility.

This database is not suitable for assessing factors influencing FP and fertility. It does not provide information on various factors which can influence: 1/patient decision such as: tumor characteristics, parity before breast cancer, desire for pregnancy, access to fertility counseling; 2/the possibility of FP such as anti-mullerian hormone level; 3/reuse of gametes such as: results of oocyte retrievals, quality of embryos. In such study, based on claim database, it was not possible to review all medical records. Because of lack of data on these potential confounding factors, we did not attempt to compare live birth rates between groups. However, we could partially consider the different follow-up times using Kaplan-Meier curves, and the age using indirect standardization.

Furthermore, we could have lost.

5. Conclusion

Oncofertility has grown over the past decade particularly after implementation of Cancer Plan in 2014. However, still small proportion of patients of childbearing age treated for breast cancer with adjuvant chemotherapy undergo FP. Despite reassuring data regarding FP and pregnancy after breast cancer, birth rate remained low. Informing all patients about infertility risk, available options for FP and possibility of pregnancy after breast cancer should be an essential aspect of supportive care of young women with breast cancer. Live births after cancer mainly resulted from spontaneous pregnancies in both groups. These data could be considered to discuss benefit-risk balance of FP, particularly in case of gonadotoxic treatment emergency, or alternative for radical surgery (neo adjuvant chemotherapy). Indeed, after ovarian reserve assessment, if healthpractioners and patients consider that chemotherapy should be first priority, potential decrease in future fertility could be accepted given the chances of spontaneous pregnancy. Further prospectives studies are necessary to confirm our results and evaluate the factors influencing the use of FP.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2022.05.006>.

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