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## **Assessment of female fertility preservation in Auvergne 3 years after implementation of the PREFERA platform (PREservation FERTilité Auvergne)**

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## **Assessment of female fertility preservation in Auvergne 3 years after implementation of the PREFERA platform (PREservation FERTilité Auvergne)**

### **INTRODUCTION**

Approximately, 177,400 new cases of cancer in women were diagnosed in 2018 in France, with 2,500 new cases reported in children and adolescents per year. Oncological treatments have led to significant improvements in survival rates. It is estimated that around 3.8 million people aged 15 and over have recovered from cancer in their lifetime, a number of whom face fertility-related sequelae.

Several factors may be responsible for impaired fertility, due to their impact on ovarian reserve; age at diagnosis [1], the disease itself [2,3], anti-cancer treatments such as gonadotoxic chemotherapy and radiotherapy, the effects of which are linked to the site of irradiation and the dose delivered [4,5]. Certain pathologies also lead to a postponement of the pregnancy project, for example breast cancer requiring hormone therapy [6]. Only surgery is experiencing a therapeutic de-escalation, with the development of conservative treatments (cystectomy, trachelectomy, uterine conservation), considered as a fully-fledged technique of preservation.

The question of fertility preservation is now an integral part of cancer management, because although the possibility has existed since the bioethics laws, the 3rd cancer plan (2014-2019) has specified the obligation of systematic information from the announcement consultation, the need for multidisciplinary consultation meetings, access to clinico-biological preservation platforms and insists on the need to promote research on this subject. Several fertility preservation techniques currently exist but oocyte vitrification (OV) is considered as a standard technique [7] according to ASCO recommendations (American Society of Clinical Oncology). However, this option can only be offered to pubescent patients for whom there is a window of time prior to the start of ovarian stimulation treatment. The second technique is ovarian tissue cryopreservation (OTC), which is the only option for pre-pubertal girls [8], or for patients who require emergency treatment or have a contraindication to ovarian stimulation. The technique involves surgical collection of ovarian fragments containing follicles to be frozen. Its results depend on the possibility of reimplantation of these fragments, limited in some cases by the risk of reintroducing neoplastic cells during the graft [9]. Finally, other techniques such as IVM (in vitro maturation), ex-vivo maturation and the use of GnRH analogs have been described, but have not yet proven their effectiveness.

In order to facilitate access to these techniques, clinic-biological platforms have been created. In Auvergne, in response to considerable demand, the PREFERA platform (PREservation FERTilité Auvergne) was created in March 2016. It allows the centralization of requests from thirty-seven regional structures, whether public or private. It is composed of biologists, gynecologists, a coordination nurse, psychologists, a sexologist, administrative support and referral doctors in various specialties, which ensure multidisciplinary collaboration. The main objective of this study is to evaluate the evolution of the preservation activity before and after the implementation of the PREFERA platform.

### **MATERIAL ET METHODS**

This is an observational cohort study whose objective is to carry out an assessment of female fertility preservation activity in the Auvergne region, carried out at the AMP-CECOS clinical-biological centre of the Clermont-Ferrand University Hospital, from March 2013 to March 2019, i.e. 3 years before and 3 years after the implementation of the PREFERA platform. The study was approved by the BLEFCO Institutional review board (IRB BLEFCO IORG00A0582).

Inclusion criteria were: Minor or adult patients aged 43 years or less, suffering from a benign or malignant pathology whose treatments were likely to impair the ovarian reserve and subsequent fertility. All doctors involved in a patient's care could request access to the platform by means of a liaison form, telephone call or e-mail.

As soon as possible, a consultation with a gynecologist was organised to provide clear information on the pathology and its consequences on fertility, to evaluate the ovarian reserve (antral follicle count by ultrasound and hormonal assessment with AMH dosage proposed), to explain treatment methods in case of preservation and to organize gynecological follow-up. In the case of fertility preservation, a consultation with the biologist took place for technical explanations, the collection of consents and the prescription of medico-legal tests such as serologies (hepatitis B, C, syphilis and HIV). Finally, consultations with a psychologist and a sexologist were systematically proposed. The different fertility preservation strategies offered in our centre were: oocyte vitrification, Ovarian tissue cryopreservation (OTC) tissue and in vitro maturation (IVM was done in collaboration with the Jean Verdier Hospital in Bondy).

In cases of oocyte vitrification, all patients presenting with a malignant disease or a therapeutic emergency received a stimulation protocol with GnRH antagonists according to the "Random Start" principle, so as not to delay oncological treatment. For patients managed for a benign disease and no emergency context (endometriosis, ovarian cysts), a long agonist type protocol was also proposed. For patients treated for hormone-dependent breast cancer, treatment with anti-estrogens (Tamoxifen®) for the duration of the stimulation was set up, under the cover of the national PHRC PRESAGE. Prior to PHRC inclusion, IVM and/or CTO were proposed. Following the puncture, the mature oocytes collected were vitrified with the RapidVit™ Oocyte kit (VITROLIFE®) January 2018 and then with the RapidVit™ Omni kit (VITROLIFE®) after February 2018. Regarding OTC, in the pubescent patient, unilateral or bilateral ovarian cortex retrieval was performed laparoscopically, in the pre-pubescent patient oophorectomy was performed instead. Cryopreservation was achieved using a slow freezing technique, with Nano-Digitcool.

Systematically, after the implementation of PREFERA, a follow-up consultation in the department was proposed to the patients 12 months after the end of the potentially gonadotoxic treatment and then on an annual basis with the aim of evaluating the ovarian reserve, the potential for spontaneous fertility and ensuring gynecological follow-up. When the remission of the pathology was proven and in the event of a desire for pregnancy, the reuse of the self-preserved products could be envisaged with the agreement of the oncologists, either by oocyte reheating and IVF/ICSI in the event of VO, or by carrying out an ovarian cortex graft. Use of cryopreserved fragment by orthotopic graft was permitted by a National PHRC called PERIDATOR

Statistical analyses were performed using Stata software (version 13; StataCorp, College Station, Texas, USA), with a two-sided type I error risk of 5%. The population was described in terms of number of individuals and associated percentages for categorical variables, and by mean  $\pm$  standard deviation or median [interquartile range] for quantitative variables, with respect to their statistical distribution (normality tested using the Shapiro-Wilk test). Qualitative

criteria were compared according to period (before or after set up of the platform) using the Chi2 or Fisher's exact test.

## RESULTS

During our study, 205 patients were referred for a fertility preservation consultation, 77 consultations took place before the implementation of PREFERA and 128 after, corresponding to an increase of nearly 66%. 169 (88.9%) patients were treated, of average age of 25.3 years (from 2 to 39 years) and 18.9% were minors (n=32). Four types of management were proposed, namely: OV alone, OTC alone, combination OV+OTC and IVM in collaboration with the Jean Verdier Hospital (Bondy). A procedure with planned OV was proposed in 113 patients, 39 were managed before the PREFERA platform was set up and 74 afterwards, corresponding to an increase of 89%. Concerning the 47 patients scheduled for OTC alone, the rate of progress was 35% before and after the implementation of the platform; and 5 patients benefited from a combination of the 2 techniques. Finally, 3 patients underwent IVM before PREFERA was set up, then, the University Hospital had joined the PHRC PRESAGE which authorized ovarian stimulation of breast cancers (Figures 1 and 2)

A total of 127 ovarian stimulation cycles were started with a view to an OV, with oocyte accumulation in 6 patients. The average stimulation time was 11 days [ $\pm 2.8$ ] and the average gonadotropin dose was 2261 [ $\pm 806$ ] IU per cycle. The mean number of vitrified oocytes (MII) was 8, (range: 0 to 29). For OTC, 46 cortex samples were obtained by laparoscopy and seven by laparotomy. Twenty-four samples were obtained after initiation of chemotherapy treatments, with an average of 23 cortex fragments frozen per patient.

Overall, 41% of patients were referred by the university hospital, 24% by the cancer center, 12% by private clinics, 9% by peripheral hospitals and 3% were referred outside the region. For 11% of patients, this information was not found. The most significant increase after the implementation of the platform concerned peripheral hospitals with a rate of change in referrals of 2.5. After PREFERA was set up, there was a sharp increase in the number of patients referred by the various specialists was recorded, with respective evolution rates of 45% to 150% (oncologists, gynecologists, hematologists, internists and others). Only the number of patients referred by pediatrics remained stable, but this department had been aware of the problem for some time. (Figure 3)

Among the patients referred for consultation, 41% were concerned with gynecological cancer, principally breast cancer, followed by borderline and rare ovarian tumors. In second place, for 30.1% of cases were hematological malignancies, with a predominance of Hodgkin's lymphoma, followed by non-Hodgkin's lymphoma and leukemia. Approximately 12.8% of the patients had a solid malignant tumor other than gynecological, including 4.4% of tumors of the digestive system, 3.4% of Ewing's sarcoma and soft tissue and 5% of other tumors (brain, ENT, lung, melanoma ...). The remaining patients were referred for non-oncological conditions: 9.6% benign gynecological pathologies (ovarian cysts, endometrioma), 4% autoimmune pathologies, some of which required alkylant treatment, 1.5% for familial or individual genetic abnormalities (Turner mosaic syndrome, familial Li Fraumeni syndrome and genetic immune deficiency) and 1% for idiopathic ovarian failure. Figure 4 shows the number of patients referred for FP consultations before and after the launch of PREFERA according to the pathologies presented. The benign pathologies had the highest rate of change after the platform was set up (x4.7; +467%). The average time between the request and the consultation in our department was 4 days [ $\pm 5$ ] for oncological pathologies. For benign pathologies, the average time was 34 days [ $\pm 30$ ].

As our platform wish to ensure patient follow-up, a post-treatment consultation was systematically proposed. In our work, this consultation was only carried out in 54 patients (26.3%) and the majority of patients were followed up after the launch of PREFERA (33% vs. 8%,  $p < 0.001$ ). A significative decrease in antral follicle count (AFC) was found after treatment, justifying the interest of this fertility preservation and the importance of subsequent follow-up (Figure 5). At the end of our study, only 2 patients (1.2%) had presented for reuse of their vitrified oocytes and only one patient in our series had benefited from an ovarian transplant; two others are waiting. There were 22 spontaneous pregnancies in 19 patients (9.3%), mostly patients treated for Hodgkin's lymphoma (6 patients) or with gynecological cancers. Finally, according to our data, seven patients (3.4%) died during our follow-up.

## DISCUSSION

One of the crucial points in the development of fertility preservation for adult women in France has been the development of vitrification. For many years, only slow freezing was possible for oocytes, but, concerns about the lack of reproducibility of results, low survival rates, polyspermic fertilizations, and the risk of embryonic aneuploidy led to a discontinuation of the activity [10]. New technique called vitrification was evaluated in the late 1990s in humans and the first live birth after oocyte vitrification was reported in 1999 by Kuleshova et al [11]. It is an ultra-rapid freezing technique, obtained by a combination of high concentrations of cryoprotectants associated with ultra-rapid cooling rates down to  $-196^{\circ}\text{C}$  [12]. In view of the promising results of this new cryopreservation technique in terms of oocyte survival, fertilization and pregnancy, the first oocyte banks were set up in Spain and USA and in the same time, oocyte vitrification for fertility preservation was developed world wide since the early 2000s [13]. Unfortunately, in France it was not authorized in France until 2011, and adult women only could be offered embryo preservation (but impossible if single woman) or OTC with less chances of reutilization. Oocyte vitrification is now recognized and practiced in France as the best preservation technique if it is possible and in 2013, the AMP-CECOS service in Clermont Ferrand started to perform oocyte vitrification for all egg donation and fertility preservation.

The increase in survival rates after cancer is indisputable, and although pregnancy rates in cancer survivors are reduced by 40% when compared to the general population (70% in breast cancer) couples clearly opt to conceive rather than resort to alternatives such as adoption or oocyte donation [14]. Providing systematic information to these patients on potential risks to their fertility and possibilities of fertility preservation is now a medical and legal obligation (3rd cancer plan). However, a review of the literature published by Goossens et al [15] showed that the proportion of patients informed about these issues ranged from 0 to 85%; the female sex being a factor of less information. Among the reasons mentioned were: concern about a delay in initiating oncological treatments, fear of procedures with the idea of a harmful effect on prognosis (particularly for hormone-dependent cancers) or the difficulty of referring patients to reproductive specialists [16]. However, these reservations are unjustified, according to Pavone et al [17], the use of "Random Start" protocols allowing stimulation to be started independently of the phase of the cycle does not delay the start of treatment without impacting on the number of oocytes vitrified. In terms of recurrence of pathology or survival, many studies have shown that access to preservation strategies does not lead to an increased risk [18].

The reluctance of professionals mainly concerns the management of prepubertal patients and those with breast cancer. Concerning the latter, requests for fertility preservation are frequent because three phenomena can lead to alteration of fertility: gonadotoxicity linked to chemotherapy, physiological ovarian ageing in the case of hormone-dependent tumors for which patients must receive hormone therapy, thus delaying the pregnancy project, and the effect of the oncological pathology itself on the ovarian reserve, even if this fact is not clearly established [19]. For a long time, hypoestrogenism, as a consequence of ovarian stimulation, was considered to be a risk for the disease and resulted in the absence of preservation or in the freezing of ovarian cortex, with the possibility of reuse of these grafts questioned by the risk of ovarian metastasis, particularly in patients with genetic mutations such as BRCA. IVM was then presented as a possibility of preservation in these patients because it allows emergency management without stimulation. However, only a few centers are authorized in France, as the puncture procedure is more difficult and the results are generally less good than in IVF [20]. Another possibility has been to propose embryo preservation on a natural cycle. However, faced with the prospect of low chances of subsequent pregnancy with only 0.6 embryos preserved per patient compared with 6.6 after stimulation; in 2003, Otkay et al. suggested the interest of prior ovarian stimulation in breast cancer [21]; many studies have reported reassurance on this subject. In order to limit hormonal elevation, it has been recommended that ovarian stimulation should be carried out under cover of protection by anti-estrogens (Tamoxifen®) or anti-aromatases (Letrozole®) [22]. It is in this sense that we have joined the research protocols allowing this stimulation, which explains the increase in our activity in this field. Unfortunately, recently the ANSM (French medicament agency) has warned of the potential mutagenic risk of tamoxifen in animals, a delay of 9 months between cessation and conception is recommended and the use of oocytes harvested with this treatment is currently under review.

A difficulty facing prepubertal patients is that there is only one proposed preservation method, namely OTC, for which it is known that in certain pathologies, there will be a contraindication to transplantation linked to the risk of recurrence within the graft, as in the case of certain acute leukemias or certain sarcomas [23]. Related research into preservation techniques (creation of artificial ovaries, ex and in vivo maturation, stem cells) or in reducing the gonadotoxicity of anticancer treatments (gonadal protectors, nano encapsulation of chemotherapies), is part of the national objectives and should be pursued [24;25].

The first platform at national level was ONCO-PACA Corse "Cancer and Fertility" created in May 2012. In the Auvergne region, PREFERA was created in March 2016. The establishment of our platform has facilitated access to information for patients and professionals through the organization of information meetings, the creation of an information leaflet and active participation in sports and charity events in association with the departmental cancer leagues. This has resulted in a 66% increase in the number of fertility preservation consultations, with an 89% increase in our VO activity and a 35% increase in OTC. The positive influence of our fertility preservation programme is in line with what has already been shown in the literature [26,27]. Although the number of female fertility preservation has increased considerably since the platform was set up, our figures may still seem low. This can still be improved, if Auvergne remains a small region of 1,3 million inhabitants, the distribution of the population is very unequal on the territory and the majority of the patients addressed to PREFERA come from Puy de Dome and little from the other departments in spite of the work of information made. Moreover, the creation of the platform was set up during the 3rd cancer plan with the help of the League and was therefore initially focused on the management of cancer pathologies as gynecological cancer and hemopathy while colorectal and lung cancers are underrepresented, despite being respectively the second and third cause of cancer in women

in 2018. More recently, however, information has been extended to other specialities and in particular to gynecologists in the context of benign gynecological pathologies, which is also apparent in our study. But efforts must be continued in this direction, notably with the French PREFERBE [28] recommendations for FP in benign gynecological diseases, and also in the context of autoimmune diseases, digestive cancers and transplantation units.

Concerning the follow-up of our patients, a large proportion of those initially referred have not been seen again, and if the relapse of the pathology or the achievement of a spontaneous pregnancy are at the origin of certain cases of non-return, this does not explain everything. Post-treatment support for these patients remains essential, whether for monitoring of fertility or for routine gynecological follow-up. In addition to the management of a desire for pregnancy, the introduction of suitable contraception and the management of possible sexological problems are all aspects to be taken into consideration. Finally, during our study, few patients (1.8% for VO) returned to use their self-preserved material. This low trend, previously observed in men, is in line with most publications like Martinez et al [29] reported a rate of reuse of 3% after a 5- year follow-up. Other authors have however reported higher levels of reuse of self-preserved material with Cardozo et al [30] reporting 36.8%, although these correspond to longer follow-up periods (17 and 10 years respectively). The low rate reported in our study may be explained by our short follow-up period, but lends support to the creation of national reuse registers.

In conclusion, fertility preservation is an integral part of the care protocol in case of potentially gonadotoxic treatment with, since the 3rd cancer plan, the setting up of regional platforms such as PREFERA. However, despite these platforms, there is still inequality of access to care across the country, a lack of knowledge on the part of certain specialists and difficulties in monitoring patients. It is therefore necessary to continue to raise awareness and provide information on fertility issues to both patients and health professionals.

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Figure 1: Flowchart of Fertility Preservation activity from 2013 to 2019

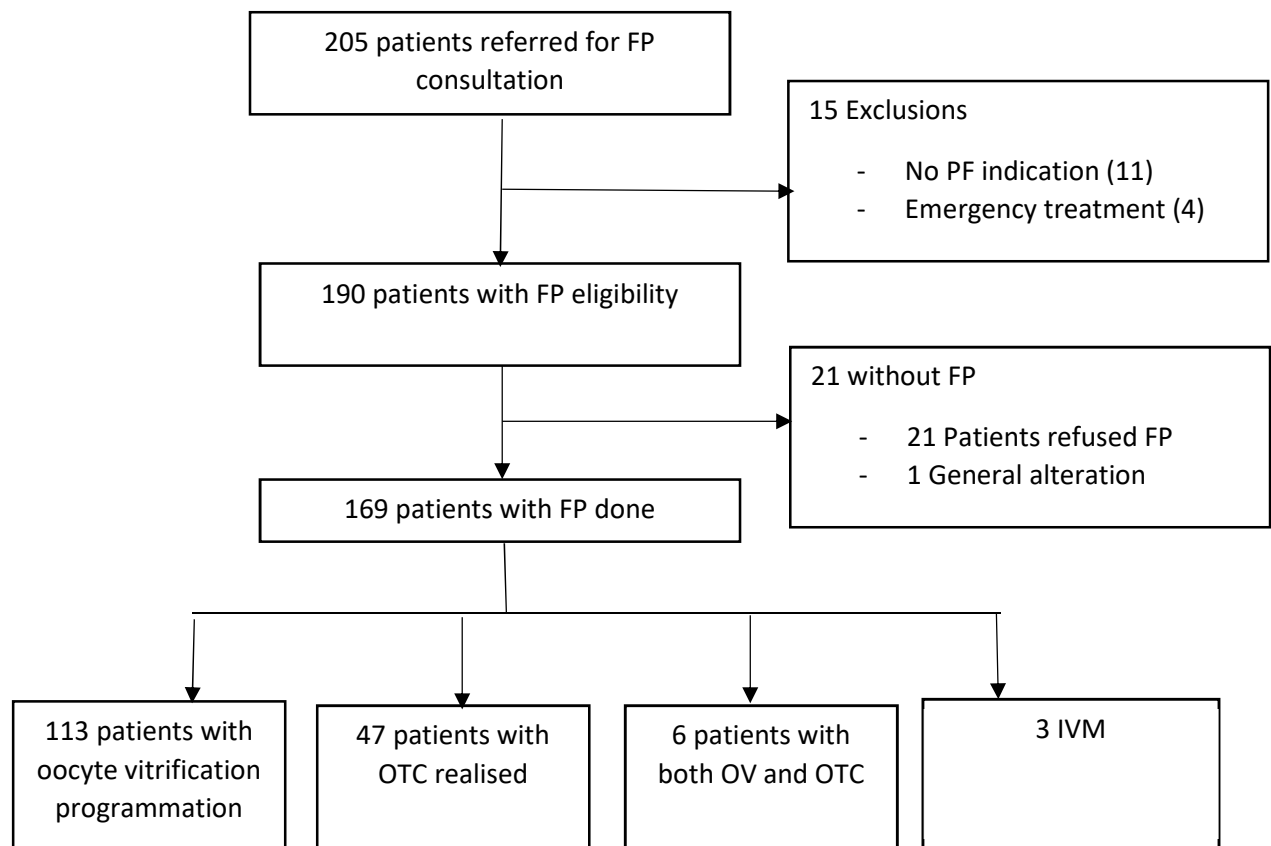
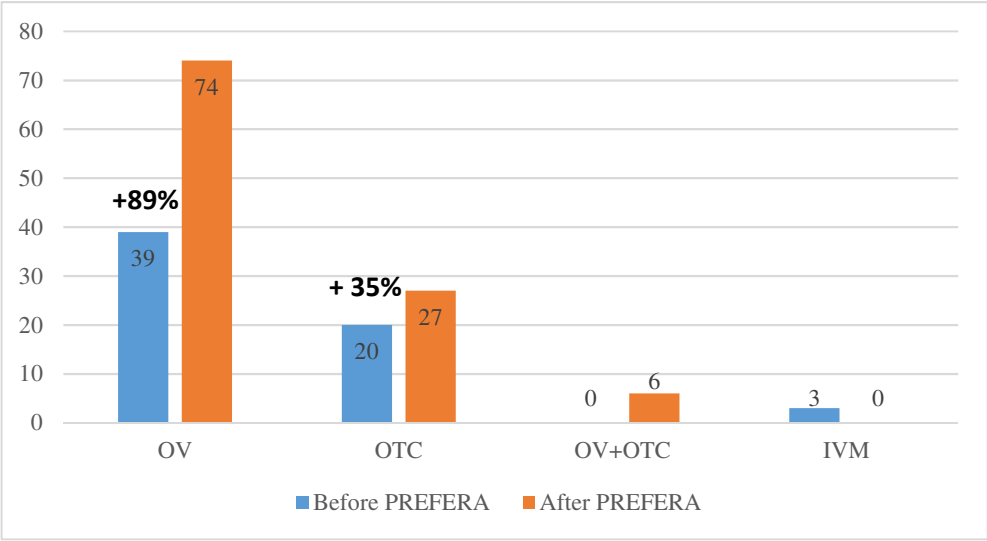


Figure 2: Number of Fertility Preservation according to the technique used before and after PREFERA creation



(OV: Oocyte vitrification, OTC Oocyte tissue congelation, IVM In vitro Maturation)

Figure 3: Number of specialists referring patients before and after PREFERA

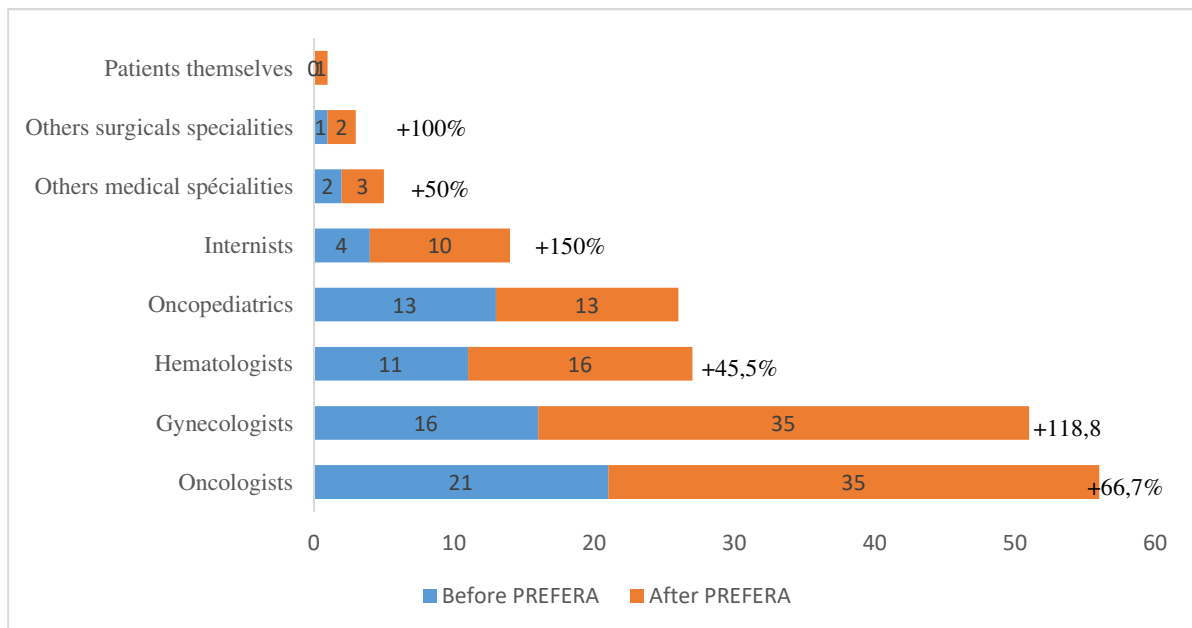


Figure 4: Number of patients referred for consultation before and after PREFERA According to their pathology

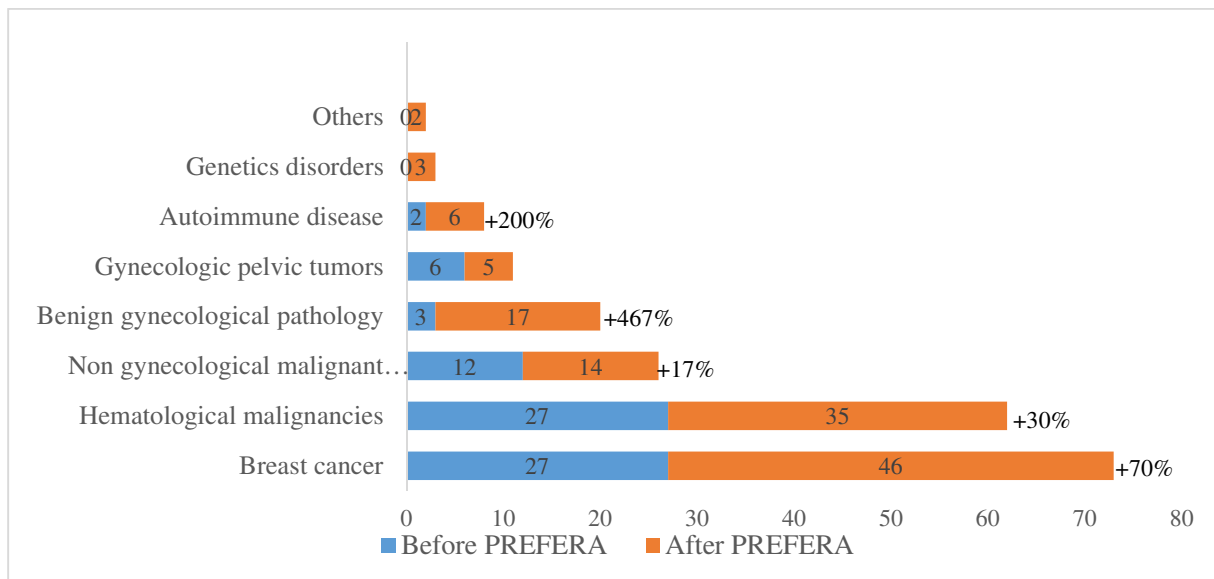


Figure 5: AMH and CFA levels before and after Fertility Preservation (FP)

	Before FP	After FP	<i>p value</i>
AMH (n=9)	3.4 [ $\pm$ 2.3]	1.6 [ $\pm$ 3]	0,09
AFC (n=22)	19 [ $\pm$ 13]	10 [ $\pm$ 7]	<0.001

*AMH (Antimullerian hormon), AFC (Antral follicle count)*