Contraception after breast cancer: a retrospective review of the practice among French Gynecologists in the 2000's

A.S. Hamy[1,2], H. Abuellellah[1], H. Hocini[1,2], F. Coussy[1,3], A. Gorins[1,2,3], D. Serfaty[2,3,4], B. Tournant[1,2], F. Perret[1,2], S. Bonfils[1,2], S. Giacchetti[1,2], C. Cuvier[1,2], M. Espie[1,2,3,4]

[1]Centre des maladies du sein, Hôpital Saint Louis, AP-HP, Paris
[2]Groupe d'Etude et de Réflexion sur les Mastopathies, Hôpital Saint Louis, AP-HP, Paris
[3]Société Française de Gynécologie; [4]Fédération Nationale des Collèges de Gynécologie Médicale, Paris (France)

Summary

Purpose of investigation: To describe the French practices regarding contraception after breast cancer in the 2000's. *Materials and Methods:* A total of 2,500 forms were sent to gynecologists practicing in France. Inclusion criteria were premenopausal patients who had a history of breast cancer and who had been prescribed contraception after diagnosis. Between June 1, 2002 and January 1, 2003, 197 evaluable responses were retrieved. *Results:* The median age of the sample was 38.5 years. The most commonly used form of contraception was an intrauterine device (n = 144, 73.1%). Hormonal contraception was prescribed for 42 patients (21.3%), and other methods were used in 29 patients (14.7%) (Condoms n = 14, tubal sterilization n = 7, and others n = 8). Recurrence occurred in 27 patients (13%); 2.9% in the progestin group, 16.3% in the IUD group, and 14.8% with the other methods). *Conclusions:* It is necessary to evaluate current contraception practices after breast cancer to evaluate the efficacy and safety of contraception in these patients.

Key words: Breast cancer; Contraception; Progestagens; Progestins; Levonorgestrel IUD-intra uterine device.

Introduction

Breast cancer among young women is a major public issue. Of women who are diagnosed with breast cancer, 25% to 30% are premenopausal, and a majority of those patients will undergo chemotherapy. In most case control studies in the literature, pregnancy after breast cancer does not seem to affect malignancy prognosis [1-5]. Nevertheless, when desired, it must be carefully planned in the setting of active counseling by a multidisciplinary team [6-7]. For patients who do not wish to become pregnant, pregnancy should be actively avoided, particularly during tamoxifen treatment, as this medication is known for its teratogenic effects [8]. Moreover, chemotherapy-induced amenorrhea might be associated with an unpredictable resumption of menses, which may result in an unwanted pregnancy. Thus, efficacious, safe and well-tolerated contraception remains of substantial interest in this population. Classical options, solely based on guidelines, include intrauterine devices (IUD), or local methods. Little is known regarding the use of progestins-estrogen or progestatin only contraception. The aim of this survey was to describe the French practice regarding contraception after breast cancer in the early 2000's. The rate of relapse in this population was also assessed.

Materials and Methods

The authors conducted a retrospective study between June 1, 2002 and January 1, 2003. A total of 2,500 forms were sent once to members of the following three French gynecologist organizations: GERM (Groupe d'Etude et de Reflexion sur les Mastopathies), FNCGM (Fédération Nationale des Collèges de Gynécologie Médicale), and SFG (Société Française de Gynécologie). Patients were included during routine gynecologic consultation. Inclusion criteria were a previous history of premenopausal breast cancer and subsequent contraceptive prescription during the six months period of the study.

Physicians were asked to return forms anonymously after retrieving data on patients who matched the inclusion criteria from their own medical records. No financial or material compensation was granted from returning forms. Breast cancer treatments were delivered primarily in French institutions. Demographic data, patient characteristics, tumor characteristics, and relapses were collected into Excel spreadsheets.

Because of the long follow-up period, some patients may have used several contraception methods. Thus, the time interval of use for each contraceptive method was recorded. To assess relapses based on contraception methods, patients were classified according to the contraceptive they had used for the longest period of time. Given the design of the study, patients who died during the time interval between prescription of contraception and the date of study were not included. In addition, due to its descriptive nature, no statistical testing was performed.

Results

A total of 204 responses were obtained. Seven patients were excluded (no contraception n = 5, missing data n = 1, and menopause n = 1). Results were obtained for 197 patients. Patient characteristics, tumor characteristics, and the treatment modalities utilized are summarized in Table 1.

The median age at cancer diagnosis was 38.5 years, and the median follow up period was 43 months. A high majority of patients had a history of a previous pregnancy

Revised manuscript accepted for publication April 23, 2013

Table 1. — *Patients, tumor characteristics, and treatments.*

Total number of patients	197	%
Median age at inclusion	43.5	
Median age at cancer diagnosis (min-max)	38.5	(24-51)
Previous pregnancy		
No	19	9.6%
Yes	170	86.3%
Parity at breast cancer diagnosis		
Nulliparous	24	12.2%
Parous	165	83.8%
Familial breast cancer history		
No	153	77.7%
Yes	44	22.3%
Clinical tumor size		
T0	6	3.0%
T1	89	45.2%
T2	42	21.3%
T3	7	3.6%
T4	3	1.5%
Histological type		
Invasive ductal carcinoma	166	84.3%
Invasive lobular carcinoma	10	5.1%
Ductal carcinoma in situ	19	9.6%
Others types	2	1.0%
Total number of invasive carcinoma	178	
Pathological nodal status		
Node positive	37	20.8%
Node negative	87	48.9%
Unknown	54	30.7%
Grade SBR		
1	27	15.2%
2	71	39.9%
3	53	29.8%
Hormonal receptor		
Negative	39	21.9%
Positive	101	56.7%
Chemotherapy		
No	57	32.0%
Yes	121	68.0%
CMF	4	
Anthracyclines based regimen	76	
Taxanes containing regimens	5	
Others	36	
Endocrine therapy		
No	100	56.2%
Yes	78	43.8%
Tamoxifen	65	
Tamoxifen and GnRH agonists	8	
Others	5	
Radiation therapy (both invasive and in situ n = 197)		
Yes	154	86.5%
No	24	13.5%

Missing data are: previous pregnancy n = 8; parity n = 8; clinical tumor size n = 50; nodal status n = 54; grade n = 27; hormonal receptor n = 38; radiation therapy n = 19.

(86.3%) and had one or more children (83.8%). When staged, tumor size was mostly small (T1: 45.8%). Pathologic characteristics showed rather invasive (89.4%), node negative (48.9%), and hormone receptor positive (56.7%) tumors. Treatments included chemotherapy (68%) and endocrine therapy (43.8%).

Table 2. — *Type of contraception in 197 patients.*

	Number of patients		Mean duration (months)
Intrauterine device (IUD)	144	73.1%	31.5
Copper IUD	*107*		
Levonorgestrel releasing IUD	*9*		
Both	*5*		
Not specified	*23*		
Progestins	40	20.3%	32
Macroprogestins	35		
nomegestrol acetate	*12*		
chlormadinone acetate	*10*		
promegestone	*6*		
medrogestone	*3*		
not specified	*4*		
Microprogestins	5		
Combined oral contraceptive	2	1.0%	NP
Others	29	14.7%	18
Condoms	14		
Tubal sterilization	7		
Spermatocidal agents/others	6		
GnRH agonists	2		
Total	197		

The sum of the different contraceptions differs from the number of total patient, because some patients may have used several contraceptive methods.

The most commonly used contraceptive was an IUD (total n = 144, levonorgestrel releasing IUD n = 14). Hormonal contraception was prescribed in 42 cases (progestins n = 40 or combined oral contraceptive n = 2), 18 of whom had hormone receptor positive tumors. Other methods (e.g., tubal sterilization, condoms, other local contraception, and GnRH agonists) were used in 29 patients (Table 2).

The authors categorized the sample into three groups: IUD, progestins, and other methods. A trend towards a longer follow up was seen in the progestin's group (median follow up: 55 months vs. 43 months (IUD) and 31 months (other methods), respectively, with a lowest rate of grade 3 (11.4% vs. 31.1 and 25.9%, respectively) and node positive tumors (5.7% vs. 22.2 and 18.5%, respectively). After a median follow up of 43 months, 27 patients (13.7%) underwent relapses (ipsilateral (n = 10), contralateral (n = 2), distant (n = 11) or non stageable (n = 4) recurrence). The rates of relapse were 2.9% in the progestin group, 16.3% in the IUD group, and 14.8% with the other methods (Table 3).

Discussion

To the authors' knowledge, this study is one of the first to date to evaluate the current contraceptive practices after a diagnosis of breast cancer [9]. There is currently little data concerning this area of research in the existing literature. In a survey of 20 cancers survivors (90% of whom had breast cancer), Patel *et al.* [10] found that 55% of the women (n = 11) were using some type of contraception, with abstinence

Table 3. — *Relapses according to patients characteristics and contraception type.*

Total 197	IUD 135	%	Relapse 22	Progestins 35		Relapse 1	Others 27		Relapse 4
Relapse rate (%)			16.3%			2.9%			14.8%
Median follow up (months)	43			55			31		
Mean age at treatment	42.9			44.7			42.9		
Histological type									
in situ	14	10.4%	4	3	8.6%		2	7.4%	1
invasive	121	89.6%	18	32	91.4%	1	25	92.6%	3
Tumor size									
T0	5	3.7%	1	1	2.9%				
T1	57	42.2%	1	19	54.3%		13	48.1%	
T2	25	18.5%		8	22.9%		9	33.3%	1
T3	7	5.2%	2						
T4	3	2.2%							
NP	38		18	7	20.0%	1	5	18.5%	3
Grade (invasive disease only)									
1	17	12.6%	4	7	20.0%		3	11.1%	
2	47	34.8%	4	12	34.3%		12	44.4%	2
3	42	31.1%	7	4	11.4%	1	7	25.9%	
N.S.	15	11.1%	7	9	25.7%		3	11.1%	2
Nodal status(invasive disease only)									
Node positive	30	22.2%	3	2	5.7%		5	18.5%	1
Node negative	58	43.0%	9	14	40.0%		15	55.6%	1
NP	33	24.4%	10	16	45.7%	1	5	18.5%	2
Hormonal receptor									
negative	34	25.2%	10	5	14.3%	1			
positive	68	50.4%	7	15	42.9%		18	66.7%	3
NP	19	14.1%	5	12	34.3%		7	25.9%	1

Note: when several contraception were reported for one patient. she was classified according to the method used the longest period. Combined oral contraception is not reported in this Table because the two patients had taken another contraception method any longer

as the preferred method (n = 6, 54.6 %). In the present survey, the most commonly used contraception was IUD, as is often recommended by expert panels [11]. The IUD represents an effective, low cost, and long term contraceptive method that can be used without problems with compliance. In women with breast cancer, its additional lack of theoretical interaction with hormonal and oncologic pathways designates it as the gold standard for contraception. However, its use may be limited by inability to tolerate the device and abnormal bleeding patterns due to unfavorable myometrial or endometrial conditions. It may also aggravate bleeding disorders during menstrual recovery from chemotherapy-induced amenorrhea. Some authors have suggested that the levonorgestrel IUD be used [12], particularly during concomitant tamoxifen therapy. As a SERM (selective estrogen receptor modulator), tamoxifen acts as an agonist on the genital tract, and its use is associated with endometrial pathologies ranging from endometrial hyperplasia and polyps to endometrial malignancy. The use of the levonorgestrel IUD in the setting of the prevention of endometrial pathology remains to be defined. After breast cancer, one case control study compared 79 breast cancer patients using LNG IUD to a control group who did not use LNG IUD (n = 120); there was no significant difference in the recurrence rate between the groups (21.5 and 16.6%, respectively, HR 1.86; CI [0.86-4.00] [13]. However, the retrospective design of this study and the low number of patients does not provide sufficient evidence to recommend LNG IUD after breast cancer routinely. Canadian Gynecologists' societies [14] consider progestin-only contraception (including levonorgestrel IUD) as a viable option for breast cancer survivors. However, the drug is classified as unacceptable according to the WHO guidelines [11] in women with a diagnosis of breast cancer. Some patients might be unwilling to have such a device placed, while others may have contraindications to an intrauterine device.

Though its safety after breast cancer has not been demonstrated, the second most commonly used contraception was progestin, mostly as oral high dose progestagens. These results highlight specific habits with respect to contraception [15, 16]. French gynecologists have been using progestagens for a long time to treat a wide range of ''female disorders'', from menstrual and menopausal transition bleeding to mastodynia and benign breast disease. Though most of them are not labeled for use in this setting, they are also widely used as contraceptives. Their current use, based on data from a Parisian hospital service, has increased with the advent of the uniquely French specialty of medical gynecology. They are an efficient and well-tolerated contraceptive with mostly weak metabolic or cardiovascular adverse effects when compared to estrogen-containing contraceptives. As a result, consumption of progestins in

France is estimated at least ten-fold higher than in other European countries or in the US, and one quarter of French premenopausal women would have used progestagens at some point [16]. Therefore, these results clearly do not represent the prescription patterns of other countries. Moreover, this survey was conducted in the early 2000's, just before the WHI study [17], which incriminated the medroxyprogesterone acetate (MPA) portion of hormonal replacement therapy in increasing the risk of breast cancer. Until that time, progestagens had long been considered to protect the mammary gland from breast cancer [18], and studies on progestative contraception and the risk of breast cancer provided reassuring data [19-24]. It is well known that different progestagens may act differently on the mammary gland, and the deleterious results of MPA have not been confirmed with French oral progestagens [25]. However, it seems impossible that such a large number of progestagens should currently be prescribed after breast cancer.

Several other methods, including local methods, were used as contraception. Their lack of interaction with the mammary gland is noteworthy; however, their efficacy has not been explored in this context. Moreover, one must also consider the frequent alterations in sexuality seen in breast cancer survivors (sexual discomfort, fear of sexual intercourse, etc.) [26, 27]. Local methods may not represent a suitable method for couples encountering such difficulties. In the present sample, tubal sterilization was rare, but could represent an option for patients who achieved their parental project, as the hysteroscopic sterilization method, Essure®, is now available as a less invasive method than tubal sterilization.

Although the results of this study are interesting, several limitations must be highlighted. First, the low rate of responses raises concerns about the representativeness of the gynecologists surveyed. Second, the retrospective design of the study introduces many biases. The studied population might have been selected for unintentionally, as women undergoing ambulatory follow up are less likely to have metastatic breast cancer and may represent a healthier population. As the median follow up was 43 months, it can be assumed that high-risk patients who relapsed early failed to be screened. This is consistent with the weak proportion of node-positive diseases and the high rate of hormone responsive tumors, reflecting a category of low-risk patients when compared with tumor characteristics generally encountered in young breast cancer patients [28]. In the present study, the authors found no difference in the relapse rates based on contraception use. However, the study was not designed to assess relapse rates. It must be noted that a trend towards a lower frequency of recurrence was noted in the progestin group, although the median follow-up in this group was longer than in the other groups. Although not significant, the difference in node positive and grade 3 disease (lower in the progestins groups) may be relevant and probably widely overrules prognosis than contraceptive use differences. Patients who relapsed after progestins may also have been underreported due to medical/legal fears. The prescription of such drugs is indeed classically contraindicated after breast cancer. The latter hypothesis seems improbable because of the anonymous nature of the form. Another hypothesis is that progestins might effectively decrease breast cancer recurrence. The survey the authors conducted does not allow to draw any conclusions concerning the protective effect of progestagens after breast cancer. Considerable concerns have recently been raised about the impact of the progestins on the breast, and it is unlikely that randomized controlled trials will occur. In this context, our work, which does not support a deleterious effect of progestagens in this setting, although biased by multiple factors, may be the only study of its kind for a long time.

With the increase in both breast cancer incidence and cure rate, survivors are becoming much more numerous, leading to a growing burden of post-breast cancer care. Supportive care and counseling in gynecology and fertility are a major concern for these women, and contraception is an important part of this issue. To date, it is unclear whether the contraception has an effect on the evolution of breast cancer. Further data would be needed to evaluate the efficacy and safety of contraception in breast cancer patients. In this setting, contraception is a personal choice that should be discussed with the patient based on her sexuality, her desire, and her compliance. Therefore, it seems improbable that a randomized controlled trial would be conducted. Prospective longitudinal studies of contraceptive use in premenopausal women after breast cancer should be done.

Acknowledgements

The authors are grateful to all of the gynecologists who participated in the study and to Mr. Porcher for his review of this manuscript.

References

[1] Verkooijen H.M., Lim G.H., Czene K., Bhalla V., Chow K.Y., Yap K.P.L. *et al.*: " Effect of childbirth after treatment on long-term survival from breast cancer". *Br. J. Surg.*, 2010, *97*, 1253.

[2] Gelber S., Coates A.S., Goldhirsch A., Castiglione-Gertsch M., Marini G., Lindtner J. *et al.*: "Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer". *J. Clin. Oncol.*, 2001, 19, 1671.

[3] Ives A., Saunders C,. Bulsara M., Semmens J.: "Pregnancy after breast cancer: population based study". *BMJ,* 2007, *334*, 194.

[4] Kroman N., Jensen M.-B., Wohlfahrt J., Ejlertsen B.: "Pregnancy after treatment of breast cancer – a population-based study on behalf of Danish Breast Cancer Cooperative Group". *Acta Oncol.*, 2008, *47*, 545.

[5] Azim H.A. Jr, Santoro L., Pavlidis N., Gelber S., Kroman N., Azim H. *et al.*: "Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies". *Eur. J. Cancer*, 2011, *47*, 74.

[6] Chabbert-Buffet N., Uzan C., Gligorov J., Delaloge S., Rouzier R., Uzan S.: "Pregnancy after breast cancer: a need for global patient care, starting before adjuvant therapy". *Surg. Oncol.*, 2010, *19*, 47.

[7] Rippy E.E., Karat I.F., Kissin M.W.: "Pregnancy after breast cancer: the importance of active counselling and planning". *Breast.*, 2009, *18*, 345.

[8] Barthelmes L., Gateley C.A.: "Tamoxifen and pregnancy". *Breast*, 2004, *13*, 446.
[9] Schwarz E.B., Hess R., Trussell J.: "Contraception for cancer survivors". *J. Gen. Intern. Med.*, 2009, *24*, S401.
[10] Patel A., Sreedevi M., Malapati R., Sutaria R., Schoenhage M.B., Patel A.R. *et al.*: "Reproductive health assessment for women with cancer: a pilot study". *Am. J. Obstet. Gynecol.*, 2009, *201*, 191.
[11] WHO | Medical eligibility criteria for contraceptive use, available from: http://www.who.int/reproductivehealth/publications/family_planning/9241562668index/en/index.html.
[12] Gardner F.J.E., Konje J.C., Bell S.C., Abrams K.R., Brown L.J.R., Taylor D.J. *et al.*: "Prevention of tamoxifen induced endometrial polyps using a levonorgestrel releasing intrauterine system long-term follow-up of a randomised control trial". *Gynecol. Oncol.*, 2009, *114*, 452.
[13] Trinh X.B., Tjalma W.A.A., Makar A.P., Buytaert G., Weyler J., Van Dam P.A.: "Use of the levonorgestrel-releasing intrauterine system in breast cancer patients". *Fertil. Steril.*, 2008, *90*, 17.
[14] McNaught J., Reid R.L., Provencher D.M., Lea R.H., Jeffrey J.F., Oza A. *et al.*: "Progesterone-only and non-hormonal contraception in the breast cancer survivor: Joint Review and Committee Opinion of the Society of Obstetricians and Gynaecologists of Canada and the Society of Gynecologic Oncologists of Canada". *J. Obstet. Gynaecol. Can.*, 2006, *28*, 616.
[15] Madelenat P., Koskas M.: "Update on the progestin-only contraception". *J. Gynecol. Obstet. Biol. Reprod.* (Paris), 2008, *37*, 637.
[16] Löwy I., Weisz G.: "French hormones: progestins and therapeutic variation in France". *Soc. Sci. Med.*, 2005, *60*, 2609.
[17] Chlebowski R.T., Hendrix S.L., Langer R.D., Stefanick M.L., Gass M., Lane D. *et al.*: "Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial". *JAMA*, 2003, *289*, 3243.
[18] Plu-Bureau G., Lê M.G., Sitruk-Ware R., Thalabard J.C., Mauvais-Jarvis P.: "Progestogen use and decreased risk of breast cancer in a cohort study of premenopausal women with benign breast disease". *Br. J. Cancer*, 1994, *70*, 270.
[19] Shapiro S., Rosenberg L., Hoffman M., Truter H., Cooper D., Rao S. *et al.*: "Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives". *Am. J. Epidemiol.*, 2000, *151*, 396.
[20] Strom B.L., Berlin J.A., Weber A.L., Norman S.A., Bernstein L., Burkman R.T. *et al.*: "Absence of an effect of injectable and implantable progestin-only contraceptives on subsequent risk of breast cancer". *Contraception*, 2004, *69*, 353.
[21] Post-marketing surveillance of Norplant((R)) contraceptive implants: II. Non-reproductive health(1). *Contraception*, 2001, *63*, 187.
[22] Skegg D.C., Paul C., Spears G.F., Williams S.M.: "Progestogen-only oral contraceptives and risk of breast cancer in New Zealand". *Cancer Causes Control*, 1996, *7*, 513.
[23] Kumle M., Weiderpass E., Braaten T., Persson I., Adami H.-O., Lund E.: "Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study". *Cancer Epidemiol. Biomarkers Prev.*, 2002, *11*, 1375.
[24] Dumeaux V., Alsaker E., Lund E.: "Breast cancer and specific types of oral contraceptives: a large Norwegian cohort study". *Int. J. Cancer*, 2003, *105*, 844.
[25] Fabre A., Fournier A., Mesrine S., Desreux J., Gompel A., Boutron-Ruault M.-C. *et al.*: "Oral progestagens before menopause and breast cancer risk". *Br. J. Cancer*, 2007, *96*, 841.
[26] Brédart A., Dolbeault S., Savignoni A., Besancenet C., This P., Giami A. *et al.*: "Prevalence and associated factors of sexual problems after early-stage breast cancer treatment: results of a French exploratory survey". *Psychooncology*, 2011, *20*, 841.
[27] Dizon D.S.: "Quality of life after breast cancer: survivorship and sexuality". *Breast J.*, 2009, *15*, 500.
[28] Walker R.A., Lees E., Webb M.B., Dearing S.J.: "Breast carcinomas occurring in young women (< 35 years) are different". *Br. J. Cancer*, 1996, *74*, 1796.

Address reprint requests to:
A.S. HAMY, M.D.
Centre des maladies du sein
Hôpital Saint Louis
1, avenue Claude Vellefaux
75010 Paris (France)
e-mail: hamyannesophie@gmail.com