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Condensation

With the advancement in modern diagnostics many cases of breast cancer are diagnosed in women who delay childbearing. The risk of infertility is a potential hardship to be faced by the patients. There are several options for women desiring preservation of fertility, including in-vitro fertilization, in vitro maturation, and oocyte/embryo/ovarian tissue cryopreservation.

Abstract

In many modern countries of the developed world, there is an increasing trend toward delay in childbearing from 30 to 40 years of age for different reasons. Improvement of diagnostic and therapeutic methods is unfortunately concordant with the increasing incidence of breast cancer in women who have not yet completed their family. Current choice for premenopausal women is an adjuvant therapy, which includes cytotoxic chemotherapy, ovarian ablation (by surgery, irradiation, or chemical ovarian supression), anti-oestrogen therapy, or any combination of these. Although the use of adjuvant therapies with cytotoxic drugs can significantly reduce the mortality in the majority of young women with breast cancer, it raises issues of the long-term toxicity, such as induction of an early menopause and fertility impairment. The risk of infertility is a potential hardship to be faced by the patients following treatment of breast cancer. The offspring of patients who became pregnant after completion of chemotherapy have shown no adverse effects and congenital anomalies from the treatment, but sometimes high abortion (29%) and premature deliveries with low birth weight (40%) rates have been demonstrated. Therefore, the issue of recent cytotoxic treatment remains controversial and further researches are required to define a “safety period” between cessation of treatment and pregnancy. Preservation of fertility in breast cancer survivors at reproductive age has become an important issue regarding the quality of life. Currently, there

are several potential options for women facing premature ovarian failure and desiring preservation of fertility, including all available assisted technologies, such as in-vitro fertilization and embryo transfer, in vitro maturation, oocyte and embryo cryopreservation, and cryopreservation of ovarian tissue. Because increased estrogen levels are thought to be potentially risky in breast cancer patients, recently developed ovarian stimulation protocols with aromatase inhibitor letrozole and tamoxifen appear to provide a safe stimulation with endogenous estrogen. Since recently, embryo cryopreservation seems to be the most established fertility preservation strategy, providing 25 to 35% chance of pregnancy. In addition, oocyte freezing can be considered as an alternative in patients that are single and in those who do not wish a sperm donor. Although ovarian tissue harvesting appears to be safe, the experience regarding ovarian transplantation is still limited due to low utilization, so the true value of this procedure remains to be determined. Nevertheless, in clinical situations in which chemotherapy needs to be started in young patients facing premature ovarian failure, ovarian tissue preservation seems to be a promissing option of restoring fertility, especially in conjuction with other options like immature oocyte retrieval, in-vitro maturation of oocytes, oocyte vitrification, or embryo cryopreservation. It seems that in-vitro maturation is a useful strategy because it improves oocyte or cryopreservation outcome in breast cancer patients undergoing ovarian stimulation for fertility preservation.

Keywords: Breast cancer; Treatment; Fertility; Pregnancy

1. Introduction

The appearance of breast cancer increases progressively with the older age with a maximum in postmenopausal women. However, an increase in the incidence of breast cancer in women aged <40 years has been reported in recent years in many Western countries. Mean annual changes in the incidence rate for the calendar period 1995-2006 from all European cancer registries were 1.032 and 1.014 in women aged 20-29 and 30-39 years old at diagnosis, respectively [1]. In the USA, the incidence of breast cancer with distant involvement at diagnosis increased in 25- to 39-year-old women from 1.53 per 100,000 in 1976 to 2.90 per 100,000 in 2009. This is an absolute difference of 1.37 per 100,000, representing an average compounded increase of 2.07% per year over the 34-year interval [2].

In many countries of developed world, an increasing trend toward delay in childbearing from 30 to 40 years of age for different reasons (educational, professional, personal, socioeconomic, and fertility problems), in addition to improved diagnostic and therapeutic methods, is concordant with the increasing incidence of breast cancer in women who have not yet completed their family. An increased breast cancer risk with advancing maternal age at first childbirth is supported by 3,7 relative risk in women with an estimated first median age of 41 years, compared with those with an estimated first birth age of 23 years [3].

Because the incidence of premenopausal women with breast carcinoma delaying pregnancy is increasing, they may have concerns regarding preservation of ovarian function due to advanced reproductive age and whether breast cancer treatment would interfere with the outcome of later fertility. The risk of infertility and of foregoing motherhood is a potential hardship to be faced by the patients following treatment of breast cancer. Within the past 10 years there has been an increasing trend of counseling before treatment (early referral) of breast cancer patients regarding fertility preservation. Factors favoring early referrals are

older age, early-stage cancer, family history of breast cancer, and academic center involvement. [4]. Although the principles of managing breast carcinoma in young women (< or = 40 years) are the same as that for older women, breast-conserving surgery is obviously desirable in young women. However, these patients have biologically more agressive disease with an increase in the risk of local recurrence associated with conservative surgery compared with patients older than 60 years. Therefore, younger patients with early breast cancer treated with breast-conserving surgery should in particular be followed up at regular intervals so that any sign of local failure can be diagnosed early [5].

Current choice for premenopausal women is an adjuvant therapy, which includes cytotoxic chemotherapy, ovarian ablation (by surgery, irradiation or chemical ovarian supression), anti-oestrogen therapy or any combination of these. Although the use of adjuvant therapies with cytotoxic drugs can significantly reduce the mortality in the majority of young women with breast cancer, it raises issues of the long-term toxicity, such as induction of an early menopause and fertility impairment. Unfortunately, adjuvant chemotherapy regimens commonly used in the treatment of breast cancer may cause premature ovarian failure due to their cytotoxic effects on the germ cells in the ovary [5-8]. Therefore, preservation of fertility in breast cancer survivors at reproductive age has become an important issue regarding quality of life. Fertility preservation is a recently emerged field of reproductive medicine that may help protect the reproductive capability of the cancer survivors and allow them to have children in the future [9]. This paper reviews the literature regarding the influence of breast carcinoma treatment on subsequent fertility, as well as current options available for fertility preservation.

2. Surgery and radiotherapy

The two principle considerations when deciding between breast-conserving surgery versus mastectomy are the cosmetic results and the risk of local recurrence. Although breast-conserving surgery is regarded desirable in young women, Arrigada et al. [5] have found that patients aged less than 40 years at the time of surgery had a 5-fold greater risk of local recurrence compared with older patients, but the effect of young age on the risk of local recurrence was not seen with mastectomy. Similarly, in the analysis of two large trials of mastectomy versus conservative surgery and radiotherapy, Voogd et al. [10] found that patients aged less than 35 years had a 9 times higher risk of local recurrence after conservative surgery than patients older than 60 years. The most important risk factors for local recurrence after breast conserving surgery are younger age (< 35 years), infiltrating tumour with an extensive intraductal component, vascular invasion and microscopic involvement of excision margins [5,10]. Therefore, Consensus panels of the National Institutes of Health and St. Galen conference have recommended adjuvant therapy for all patients aged under 35 years, based on the evidence that they have poor prognosis [11].

The effect of radiotherapy analysed in a study by Malamos et al. [6]. showed no consequence of radiotherapy on the rate and clinical outcome of pregnancy, and at a mean follow-up of 18 months no anatomical defects were observed in the offspring. In one of the largest studies by Dow et al. [12], of 1624 patients providing information about the influence of radiotherapy on later fertility, there were 23 women who had subsequent pregnancies after the mean time of 30 months (range 6-84 months). 22 of 23 women deliveried normal full-term babies, and the remaining patient a low birth-weight infant, with no adverse clinical outcome on pregnancy subsequent to treatment. They reported only diminished lactation from the irradiated breast in those women who had undergone radiotherapy following breast-conserving surgery, which had been presumbly due to atrophy of the breast lobules. Similar problem with lactation was noticed in a series of 13 patients by Higgins et al. [13] who

reported that 1 patient successfully breast fed following surgery and radiotherapy and 3 further patients lactated from the treated breast, but were unable to breast feed.

3. Chemotherapy

With improved education and increased screening, it is likely that more women will be diagnosed with early-stage breast cancer at younger ages than ever before. Most national guidelines of early-stage invasive breast cancer with negative estrogen receptor recommend treatment with adjuvant cytotoxic therapy, and hormone therapy with estrogen positive receptor tumours. The exception to these guidelines refers to cases in which the tumours are small.Thus, the majority of young women diagnosed at early-stage breast cancer will undergo adjuvant chemotherapy. Long-term survival is likely when the breast cancer is diagnosed at an early stage, especially after adjuvant cytotoxic therapy [7].

However, another important aspect of therapy decisions in the young premenopausal women undergoing chemotherapy is the preservation of fertility. Although many of these women benefit from chemotherapy, they are afraid to risk the opportunity of bearing children, because of ovarian damage and failure, which is an important and unfortunately common long-term side effect of curative chemotherapy [14]. Indeed, after such treatments, the incidence of amenorrhea has been reported to vary from 40% to 68%. Also, the patients who recover menses after chemotherapy face the likelyhood of a premature menopause as a result of depleted follicular store. These facts represent a serious problem for these cured patients, because many of them are relatively young and have expectations of a normal reproductive life. The incidence of ovarian failure varies with factors such as the type, duration, total cummulative dose of a drug, age of the patient, and possibly on factors yet to be determined [15]. The proportion of women developing ovarian failure rises dramatically after the age of

40 years, and is irreversible in most cases. The higher grade of ovarian failure in older women might be explained by the lower number of remaining follicles [16].

The exact mechanism of chemotherapy induced ovarian failure is poorly understood. An in vitro model has demonstrated that in the human ovary chemotherapy acts primarly on primordial follicles, through the induction of apoptotic changes in pregranulosa cells, which lead to irreversible loss of follicles and oocytes, along with the evidence of fibrosis [17]. The category of the drugs most likely to induce ovarian failure is that of alkylating agents, such as cyclophosphamide and melphalan, whereas antimetabolites have a lesser effect. Combination chemotherapy is used more often than single agents, and it is therefore difficult to evaluate the contribution of each individual drug. The largest body of data on ovarian failure in breast carcinoma patients is derived from the experience with cyclophosphamide, methotrexate, and 5-fluouracil regimen [16].

In a retrospective review by Sutton et al. [18], of 227 consecutive breast cancer patients who were 35 years of age and younger, there were 33 pregnancies in 25 women after chemotherapy (of which 10 pregnancies were terminated, 2 patients had spontaneous abortions, and 19 patients gave birth to full-term offspring without fetal malformation). Two patients were still pregnant at the time of this report. The median interval between the completion of treatment and pregnancy was 12 months, and several patients became pregnant a few months after treatment. Of the 25 patients who became pregnant, recurrent disease subsequently developed in 7, and 3 died. It was concluded that in a sizeable fraction of patients aged 35 or younger treated with adjuvant chemotherapy, ovarian function remained intact, and subsequent pregnancy did not affect disease-free interval or survival of the patients. The offspring of patients who became pregnant soon after completion of chemotherapy showed no adverse effects from the treatment. With regard on teratogenicity of adjuvant systemic therapy, Doll et al. [19] have shown that if chemotherapy is administred

during pregnancy, there is 16% incidence of fetal malformations in the first trimester, but without an increase in the incidence of teratogenesis if treatment is commenced in the second or third trimester. The incidence was lowered to 6% if folate antagonists were used in combination with chemotherapy. It has been shown that adjuvant or neoadjuvant chemotherapy of breast cancer patients with antracycline (FAC protocol) can be given relatively safely in second and third trimestre of pregnancy [20, 21]. There are limited data on the use of taxanes, or trastusumab in pregnacy, so if indicated, they should be administrated in postpartal period, as well as radiation or endocrine therapy [22] In a study by Mulvihill et al. [23], it was found that the children born to women who have conceived after cytotoxic therapy, did not appear to be at higher risk for congenital anomalies. However, the study reported a 40% rate of abnormal pregnancies, mainly of premature birth and low birth weight, both of which were attributed to dysfunction of the uterine hormonal gestational milieu. In a study by Blakely et al. [24] the high rate of miscarriage (29%) has been explained by the older age of the women, and changes to ovarian function that can occur after chemotherapy. Unfortunately, the delayed effects on offspring remain to be determined on those who conceive either whilst the mother is undergoing chemotherapy or subsequently. Because the risks of recurrence are more frequent during the period of several years following chemotherapy Valle et al. [25] recommended the use of barrier contraceptives for a longer period.

4. Endocrine therapy

Adjuvant chemotherapy is frequently incorporated as the only useful adjuvant treatment into the management of premenopausal women with estrogen receptor negative breast cancer. As noted previosuly, issues of long-term toxicity from chemotherapy for breast

cancer, frequently including the induction of premature ovarian failure, appear to be of increasing importance for the survivors who become infertile due to ageing and diminished ovarian reserve. Therefore, avoidance of chemotherapy-related ovarian toxicity may provide best prospects for fertility after treatment [9, 16]. For young women with receptor-positive breast cancer, endocrine therapy including ovarian suppression-ablation with gonatrophin releasing hormone (GnRH) analogues and tamoxifen, was considered at least a legitimate alternative or complement to conventional to chemotherapy [11]. Because several clinical trials have found a definitive benefit for combined medical suppression and chemotherapy, it has been suggested that the subgroup of premenopausal patients with receptor-positive tumours who do not become amenorrheic with chemotherapy, may benefit from the adition of reversible ovarian suppression [26, 27]. Ovarian medical suppression combined with tamoxifen is currently accepted as an adjuvant endocrine treatment for premenopausal receptor-positive breast cancer. This treatment represents a reasonable alternative for women with good risk early-stage breast cancer (receptor-positive, lymph node-negative disease), particulary those wishing to preserve fertility [8]. It is strongly suggested that the associaton of GnRH agonist and tamoxifen offers excellent protection against the endometrial side effects induced by tamoxifen. Moreover, tamoxifen appears to be able to reduce the significant bone loss induced by GnRH agonist in young women [28]. However, in a recent study it was found that GnRH analogue cotreatment does not offer a significant protective effect on ovarian function in patients treated by cyclophosphamide-based chemotherapy [29]. Fertility outcomes after common adjuvant chemotherapy regimens for breast cancer by major clinical studies are presented in Table 1 [30-42].

5. Current options for fertility preservation

In recent decades there has been a progress in the field of breast cancer cytotoxic treatment, which has led to increasing numbers of survivors, but often with significant reproductive impairment. It is reasonable to assume that the preservation of future fertility is likely to be a priority for women desiring pregnancy under the age of 40 years. Therefore, there are currently several potential options for women facing premature ovarian failure and desiring preservation of fertility, including all available assisted technologies, such as in-vitro fertilization and embryo transfer (IVF-ET), in vitro maturation, oocyte and embryo cryopreservation, and cryopreservation of ovarian tissue [16, 43-60].

The first reported case of successfully achieved pregnancy using ovarian stimulation with human menopausal gonadotrophins and IVF-ET and delivery of a healthy baby was in 1992 in a patient who had primary infertility for 6 years after radical mastectomy for the invasive breast carcinoma [43]. Unfortunately, because of the fact that breast cancer cell proliferation and dissemination can be induced by the higher concentrations of estrogen, many oncologists currently consider conventional ovarian stimulation regimens to be contraindicated in these patients [44]. Because increased estrogen levels are thought to be potentially risky in breast cancer patients, natural cycle IVF in combination with embryo cryopreservation has been used to treat infertility and preserve fertility. In addition, it is known that tamoxifen, a drug of choice in breast cancer treatment and prophylaxis worldwide, has been used for the treatment of annovulatory patients for many years, but it has never been used as an ovarian stimulant in IVF cycles [45]. In order do develop a safe ovarian stimulation protocol of IVF and fertility preservation in breast cancer patients, Oktay et al. [46] compared in their study tamoxifen stimulation with natural cycles during IVF. In the group of 12 women on tamoxifen stimulation, who had IVF with either fresh embryo transfer or cryopreservation, there was a higher number of embryos in comparison with 5 patients in

natural cycles. Although in the group of patients on tamoxifen stimulation there were increased estradiol levels comparing with the patients in natural cycles, yet it was regarded that tamoxifen could reduce breast cancer incidence with its suppressive effects in these patients. In a later study the same authors [47] tried to develop other safe ovarian stimulation methods to perform IVF in breast cancer patients. Of 60 women with breast cancer 29 patients underwent ovarian stimulation with either tamoxifen alone or in combination with low doses of follicle stimulation hormone (FSH) or aromatase inhibitor letrozole in combination with FSH. It was found that tamoxifen or letrozole in combination with low doses of FSH stimulation showed similar superiority regarding on the number of embryos, in comparison with tamoxifen alone, although the letrozole protocol may be prefered because it results in a lower peak of estradiol. In a recent study, it was suggested that in the short term, aromatase inhibitors and gonadotrophins are safe and effective agents for ovarian stimulation in fertility preservation cycles, supporting the use of aromatase inhibitors for ovarian hyperstimulation in women with breast cancer before initiating adjuvant chemotherapy [48].

Although previous studies [18,19] have not shown any increase of congenital malformations in pregnancies occurring long after administration of chemotherapy, the safety of using IVF and embryo cryopreservation in breast cancer patients who have recently undergone chemotherapy is questionnable. Therefore, further research is needed to define a "safety period" between cessation of treatment and oocyte retrieval for IVF. Until definitive data are achieved, it would be useful to monitor the pregnancy outcome of all cancer patients who undergo oocyte retrieval and IVF, and possibly screen fetuses and babies cytogenetically for analyses. However, since recently embryo cryopreservation seems to be the most established fertility preservation strategy, providing 25 to 35% chance of pregnancy. In addition, oocyte freezing can be considered as an alternative in patients that are single and in those who do not wish a sperm donor. Embryo cryopreservation as well as oocyte

cryopreservation are considered standard practice and are widely available. Currently, embryo/oocyte cryopreservation obtained after controlled ovarian stimulation appears to provide the best fertility preservation option. [49]. Ovarian tissue freezing could also be an option in breast cancer patients who do not wish or have time for an IVF cycle, which requires 10 to 14 days of ovarian stimulation. In a study by Donnez et al. [50], there has been reported a livebirth after orthotopic autotransplantation of cryopreserved ovarian tissue. Recently Donnez et al. [51] concluded that transplantation of cryopreserved ovarian tissue should no longer be considered an experimental procedure, despite the fact that there have been „only“ 24 babies born among the 60 patients with reimplantation performed by three teams in the last decade. Currently, embryo and mature oocyte cryopreservation following IVF are the only techniques endorsed by the American Society of Reproductive Medicine, and other methods are still considered to be investigational [52]. The outcome of the various fertility preserving options used in cancer patients is presented in Table 2 [51, 53, 54]. In clinical situations for which chemotherapy needs to be started for young patients facing premature ovarian failure, ovarian tissue preservation seems to be a promissing option of restoring fertility, in conjuction with other options, like immature oocyte retrieval, in-vitro maturation of oocytes, oocyte vitrification, or embryo cryopreservation. It seems that in-vitro maturation is a useful strategy because it improves oocyte or cryopreservation outcome in breast cancer patients undergoing ovarian stimulation for fertility preservation [55]. Fertility preservation for breast-cancer patients using in-vitro maturation followed by oocyte or embryo vitrification calculated through pregnancy rates per vitrified oocyte and embryo were 3.8% and 8.1%, respectively [56]. The development of fertility preservation has recently opened new perspectives in the field of in-vitro maturation. The combination of ovarian tissue cryopreservation with immature oocyte collection from the tissue followed by oocyte vitrification via in-vitro maturation represents another promising approach of new trends in

fertility preservation in young women with cancer [57]. However, the risk of cryopreserving and transferring malignant cells with reimplantation remains, so screening methods with immunohistochemical markers should be developed to detect minimal residual disease. Among the different pathologies investigated, the highest risk of reimplanting malignant cells was found with leukemia. Therefore, for ovarian tissue from patients with hematologic malignancies, it is of paramount imporance to identify minimal residual disease before ovarian tissue transplantation [58]. Although the last decade has brought many options for women with breast cancer considering fertility preservation, but numerous challenges remain. The presence of BRCA mutations further contributes to these challenges and studies specific for women with BRCA mutations are lacking. Women with BRCA mutations may elect to use preimplantation genetic diagnosis during in vitro fertilization to avoid transmitting the mutation [59]. Since there are some indications that BRCA 1 mutations could be related to diminished ovarian reserve, familiar breast cancer should be the subject of further research. [60]. In the future, it is necessary to improve freezing techniques and enhance the vascular bed before implantation to increase pregnancy rates [50]. In addition, more studies are needed to determine the real role of different preservation options in breast cancer patients. Moreover, the long term influence of different breast carcinoma treatment modalities (such as longer hormonal therapy, immunotherapy or radio therapy) remains to be determined.

6. Conclusion

It is known that in the past many women with breast cancer thought that the information about later fertility they have received was either insufficient or unavailable. This information might not be actual at the time of diagnosis, but it becomes very important after diagnosis of breast cancer. Currently, several fertility-sparing options with the use of assisted

reproductive technology have been developed, and they are available before, during, and after treatment of breast cancer. Therefore, many women consider that the information about fertility should be given prior or after breast cancer treatment. Because fertility after breast cancer is a major concern for young women desiring pregnancy, the patient′s future chance of pregnancy should be maximized by organizing an appropriate assisted reproduction center with a multidisciplinary team as soon as the diagnosis is made, rather than after the treatment, to enable patients to discuss their options for fertility preservation.

Table 1. Rates of amenorrhea categorized by patient age group after common adjuvant chemotherapy regimens for breast cancer

Regimen	Study	Number of Patients	Number of cycles	Age of patients (years)	Amenorrhea (%)
CMF	Goldhirsch et al. [30]	387	6-7	≥40	81 (vs. 26% without chemo)
				<40	33 (vs. 6% without chemo)
	Pagani et al. [31]	1,196	3-9	≥40	74
				<40	18
	Castiglione et al. [32]	360	6	≥40	90
				<40	40
	Bianco et al. [33]	221	6-9 +/- tamoxifen	≥40	86
				<40	33
	Jonat et al. [34]	823	6	≥40	90
				<40	26
AC	Tramyl et al. [35]	77	4	≥40	81
				<40	44
FEC	Roche et al. [36]	169	6	≥40	73
				<40	38
	Lupors et al. [37]	249	Up to 6	≥40	88
				<40	32
Epirubicin based	Borde et al. [38].	1,103	3-6	<40	34
Anthracycline and taxane based	Ganz et al. [39]	793	4c AC -> 4c docetaxel	Premenopausal	70
		806	8c TAC		58
	Tramyl et al. . [35].	118	4c AC → 3m taxane	≥40	84
				<40	61
	Fornier et al. [40]	166	AC -> taxane (variable cycles)	≤40	13
		82	+ endocrine		17
	Samuelkutty et al. [41]	140	4c EC → 4c docetaxel	>40	86
				<40	46
	Martin et al. [42]	421	6c TAC	Premenopausal	62

Note: CMF –cyclophosphamide, methotrexate, and 5-fluorouracil; AC –doxorubicin and cyclophosphamide; TAC – docetaxel, doxorubicine and cyclophosphamide; EC-epyrubicin, cyclophosphamide; FEC-5-fluorouracil, epirubicin, cyclophosphamide; c-cycles

Table 2. The outcome of the various fertility preserving options used in cancer patients

Fertility preserving options	References	Patients	Births
Oocyte cryopreservation	Garcia-Velasco et al. [53]	355	6
Embryo cryopreservation	Barcroft et al. [54]	42	3
Transplantation of cryo-preserved ovarian tissue	Donnez et al. [51]	60	24

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