

Intrauterine contraceptive device versus barrier methods for breast cancer women undergoing postoperative chemotherapy: A randomized controlled trial

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Abstract

Objective: to compare the effectiveness of intrauterine device and the barrier methods of contraception in the form of male condom during the postoperative chemotherapy period in patients with breast cancer at the reproductive age.

Study design: A randomized controlled clinical study enrolled married patients, aged ≤ 44 years with breast cancer scheduled for chemotherapy. Group (A) (n=51) randomly used intrauterine device and group (B) (n=51) used male condom for contraception.

Results: Although patients' menstrual patterns showed no significant differences at the entry to the study, patients in group (A) showed heavier cycles when evaluated after 3m and again after 6m from the onset of the chemotherapy. The duration of bleeding (mean \pm SD) was 7.7 ± 1.7 and 5.6 ± 1.3 in group A and B respectively after 3m and significant changes in the cycle length and the duration of bleeding after 6m had occurred. Likewise, the incidence of genital tract infection was higher in the group using intrauterine device while receiving chemotherapy.

Conclusion: While intrauterine contraceptive device was always considered as the method of choice for most of the malignant patients, this study showed that it is more practical to use the barrier methods at least during the chemotherapy cycles in order to minimize the associated hazards of chemotherapy induced bone marrow depression on the safety of intrauterine device.

Key Words: breast cancer, reproductive age, intrauterine contraceptive device, barrier methods.

Introduction

Breast cancer is the most common malignancy in women, and one in eight women will be diagnosed with breast cancer during her lifetime (1). It is considered as the second leading cause of cancer mortality among women (2). While breast cancer risk increases with age, approximately 35% of breast cancers occur during the reproductive and premenopausal years (3). Although epidemiologic surveillances found that the absolute risk of breast cancer under the age of 40 is relatively low, reproductive age group women remain a very critical age while managing cancer. Surgical treatment was and continues to be the primary line for all ages but still the postoperative management; an ever-changing field, in young patients, in particular, has attracted recent interest (4). Therefore, chemotherapy is increasingly being considered appropriate for all women under the age of 35 years. However, it poses the particularly difficult problem of fertility preservation, that's why the benefits of chemotherapy need to be weighed against the possible dangers, and therapy should be individualized according to cancer pathology and patient's circumstance (5).

Alterations in menstrual function and fertility may occur in women who receive chemotherapy for breast cancer and some demonstrated that women < 35 years old resume regular cycles 2 years after treatment, with

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outcomes more variable than for women ≥ 35 years old⁽⁶⁾. Generally, the progress in diagnostic tools, care and treatments of breast cancer, increases the survival rate more than 80% at 5 years for operable stages in young women⁽⁷⁾.

While women were previously advised to postpone conceiving for two to five years after breast cancer diagnosis, newer published data does not demonstrate an alteration in survival with breast cancer to pregnancy intervals longer than 10 months⁽⁸⁾.

The strong relation described many years ago between steroid hormones and breast cancer and the high incidence of hormone receptor positive tumors, made the capability of prescribing hormonal contraception for the patients in the reproductive age, a matter of putting the patient into jeopardy^(9, 10).

From this aspect, safe, effective and suitable contraception should be discussed and made available to all women undergoing diagnosis, treatment, and follow up for breast cancer⁽¹¹⁾. In the current study, we described a protocol for a randomized controlled study to assess the effectiveness and the method related complications while using non-hormonal intrauterine contraceptive device (IUD) or barrier (male condom) contraceptives for patients at the reproductive age with breast cancer and scheduled to receive adjuvant postoperative chemotherapy.

Patients and Methods

This randomized controlled clinical study enrolled patients with hormone-receptor-positive operable invasive primary breast cancer who are scheduled to undergo post mastectomy firstline adjuvant chemotherapy at Oncology center, Mansoura University Hospital, Mansoura, Egypt, in the period from July 2010 to June 2014 and in need to use a proper contraceptive method. Patients who gave a written informed consent after receiving detailed written and verbal information were admitted to the study. Participation was voluntary and could be withdrawn by the patient at any time. The study was authorized by the Department of Obstetrics & Gynecology, Mansoura Faculty of Medicine, Mansoura University and approved by the Institutional Research Ethical Committee.

The study included married patients in the reproductive age as defined by World Health Organization (WHO) (≤ 44 years old)⁽¹²⁾. All patients were screened for eligibility during their hospital stay in the oncology center and those who met the inclusion criteria were informed about the study concept and invited by their oncologists to take part in the study. Those patients were diagnosed and treated surgically according to the

national guidelines of breast cancer management and subjected to the tumor board where 6 cycles of chemotherapy (Epirubicin, Cyclophosphamide, Fluorouracil and Taxotere) were addressed for each patient. A detailed history, general and pelvic examinations and ultrasound evaluation were carried out for all patients. Exclusion criteria were evident pelvic inflammatory disease (PID) or recent form of it, pre or post-operative history of heavy menstrual bleeding, presence of anomalies of the uterus, distorted uterine cavity by any lesions as uterine myomas. Diabetic patients were also excluded from the study being at higher risk of genital infection. Patients with active liver disease or dysfunction were also excluded because they carry the risk of bleeding tendency.

By the above rules, 102 women were included in this study and randomized to select IUD or male condom according to a computer-generated random numeric table prepared by an independent statistician with concealment of method option by the use of closed envelopes that were given to a third party (nurse) who assigned patients into 2 equal study arms each one (51); group A (IUD) or group B (male condom). In group (A): we offered copper T 380A IUD (safe load, DKT Company) for contraception where it is inserted under sterile conditions by a single gynecologist, followed by transvaginal ultrasound for post insertion assessment. Warning signs as missed period, lower abdominal pain, vaginal bleeding or discharge were informed to every patient and instructed to seek a medical advice when any occur. Azithromycin (500 mg) a single dose orally was given to all patients in this group as a prophylaxis before insertion of the IUD⁽¹³⁾. In the other group (B); patients were instructed in a session including her partner to use the male condom for protected intercourse and informed about the faulty behaviors that may lead to condom breaking, leaking, or slipping off during intercourse that predispose for method failure⁽¹⁴⁾. Data were recorded at preliminary phase of inclusion in the study then at three months and six months intervals. During this follow up periods, at 3 and 6 months, patient's history regarding the menstrual cycle pattern (subjectively assessed by the amount of menstrual blood loss, duration of bleeding and the number of sanitary towels used⁽¹⁵⁾), development of genital infection whether lower or upper, data of general examination and pelvic examination were recorded.

A "Satisfaction Questionnaire" about the method used was prepared to be fulfilled by both partners during the first visit (after 3 months) and the second visit (after 6 months) and gathered data were subjected to tabulations and analytical studies.

- Are you satisfied with the method of contraception you use?
- Do you prefer to keep using this method?
- Do you want to suggest these IUDs or male condom methods to the others?

Statistical analysis:

Statistical analysis was performed using SPSS for windows version 17.0 (SPSS, Chicago, IL). Continuous data were expressed as mean \pm standard deviation (SD). Data were checked for normality and equality of distribution, prior to any analysis being performed. Skewed continuous variables were logarithmically transformed to accomplish a normal distribution. For variables that would not reach a normal distribution by logarithmic transformation, nonparametric tests would be used. Chi square and Student t test were appropriately used and P-values < 0.05 were considered to be of statistical significance.

Results

This study included 102 women in the reproductive age divided into two equal groups. Group (A= IUD users, n=51) and Group (B= male condom users, n=51). The socio-demographic data of both groups appeared comparable with no significant difference as shown in **table [1]**. Most of the patients in both groups were with low parity, however nulli-parity was recorded in (11.8%) in group (A) and (9.8%) in groups (B). Family history of breast cancer was evaluated and found to be positive in 17.6% of patients in group (A) and in 13.7% in group (B). Invasive ductal carcinoma was identified as the predominant histological type in both groups. The tumor staging based on TNM staging (16) showed no significant differences between both groups. Menstrual cycles were regular in most of patients and the amount of bleeding described subjectively by the patients was average in more than 85% of patients in both groups.

Patients' criteria that were evaluated during the first 3 months after starting the chemotherapy are presented in **table [2]**. There is a relative increase in the number of patients with heavy cycles in group (A) (21 out of 51) versus (9 out of 51) in group (B) as well as a significant increase in the duration of bleeding among group (A). The incidence of recurrent lower genital tract infections were much higher in group (A) compared to group (B), meanwhile upper genital tract infections were found also higher in the same group using IUD. After 3 months more (6 months of starting chemotherapy), all patients were reevaluated and the data

are presented in **table [3]**. The cycle pattern showed a significant change as regard the duration and the amount of bleeding and in comparing both groups (p value is 0.001). Lower genital tract infections occurred in 29/51 in group (A) compared to 8/51 in group (B) and upper genital tract infections also remained higher in group (A).

As regard patients' satisfaction, in group (A) less number of patients were satisfied with IUDs comparing the two periods of evaluations (after 3m and after 6m) where 35.3% only were satisfied after 6 months use. On the other hand, the group (B) patients showed high acceptability and satisfaction with the condom use yet rather than their husbands. After completing the courses of chemotherapy, 15 out of 51 patients used IUD asked for changing the method versus only 5 in the group using condoms.

Table (1)

Patients' characteristics at the start of the study

Characteristics	Group A (IUD user, N=51)	Group B (condom user N=51)	P value
Age (years) Mean \pm SD	36.4 \pm 4.2	36.2 \pm 4.4	0.783
parity Mean \pm SD	1.16 \pm 0.46	1.16 \pm 0.42	0.855
Nulliparous women	6 (11.8%)	5 (9.8%)	
Occupation: HW EM	HW: 3 (66.7%) EM: 17 (33.3%)	HW: 31 (60.8%) EM: 20 (39.2%)	
Residence: U R	U: 21 (41.2%) R: 30 (58.8%)	U: 20 (39.2%) R: 31 (60.8%)	
Family history of breast cancer	Positive: 9 (17.6%) Negative: 42 (82.4%)	Positive: 7 (13.7%) Negative: 44 (86.3%)	
Age of menarche Mean \pm SD	11.6 \pm 1.7	11.3 \pm 1.3	0.200
Cycle rhythm	Regular: 46/51 Irregular: 5/51	Regular: 44/51 Irregular: 7/51	
Cycle length Mean \pm SD	31.52 \pm 8.37	29.32 \pm 6.22	0.167
Cycle duration Mean \pm SD	5.30 \pm 1.12	5.34 \pm 1.09	0.488
Amount of bleeding	Average: 45/51 Heavy: 6/51	Average: 44/51 Heavy: 7/51	
Breast cancer staging at operation	SI: 11 (21.6%)	SI: 15 (29.4%)	
	SII: 35 (68.6%)	SI: 30 (58.8%)	
	SIII: 5 (9.8%)	SII: 6 (11.8%)	
Histo-pathological type	L: 6 (11.8%)	L: 5 (9.8%)	
	D: 45 (88.2%)	D: 46 (90.2%)	

P-values < 0.05 were considered to be of statistical significance.

HW: House wife

U: Urban

EM: Employer

R: Rural

L: Lobular carcinoma

D: Ductal carcinoma

Table (2)

Patients' characteristics after 3 months of chemotherapy

Variable	Group A (IUD user, N=51)	Group B (condom user n=51)	P value
Failure rate	0	0	
cycle regularity	Regular: 33 (64.7 %) Irregular: 18 (35.3%)	Regular: 36 (70.6 %) Irregular: 15 (29.4 %)	----
Cycle Length	37.78 ±10.81	36.28 ± 8.1	0.09
Duration of bleeding	7.72 ± 1.738	5.6200 ± 1.38343	0.018
Amount of bleeding	Average:30 Heavy: 21	Average: 42 Heavy : 9	----
Lower genital tract infection	23/51	11/51	----
Upper genital tract infection	8/51	2/51	----
Patients satisfaction	38/51 (satisfied =74.5%) 13/51 (unsatisfied =25.5%)	45/51 (satisfied =88.2%) 6/51 (unsatisfied =11.3%)	----
Partner satisfaction	47/51 (satisfied =92.2%) 4/51 (unsatisfied =7.8%)	20/51 (satisfied =39.2%) 31/51 (unsatisfied =60.8%)	----
Method discontinuation	0/51	0/51	----

P-values<0.05 were considered to be of statistical significance.

Table (3)

Patients' characteristics after 6 months of chemotherapy

Variable	Group A (IUD user: n=51)	Group B (condom user n=51)	P value
Failure rate	0	0	
cycle regularity	Regular: 18 Irregular: 33	Regular: 34 Irregular: 17	----
Cycle Length	40.82 ± 10.71	49.9 ± 10.46	0.001
Duration of bleeding	3.66 ± 1.89	2.48 ± 2.31	0.001
Amount of bleeding	Average: 16 Heavy: 35	Average: 49 Heavy: 2	----
Lower genital tract infection	29/51	8/51	----
Upper genital tract infection	8/51	1 /51	----
Patients satisfaction	18/51 (satisfied =35.3%) 33/51 (unsatisfied =64.3%)	47/51(satisfied =92.2%) 4/51(unsatisfied =7.8%)	----
Partner satisfaction	40/51 (satisfied =78.4%) 11/51(unsatisfied =21.6%)	10/51(satisfied =19.6%) 41/51(unsatisfied =80.4%)	----
Method discontinuation	15/51	5/51	----

P-values<0.05 were considered to be of statistical significance.

Discussion

Based on the mandatory contraception during the post-operative adjuvant chemotherapy in reproductive age group patients with breast cancer, and the multiple different health hazards associating the chemotherapy in those patients, the choice of an ideal practical method of contraception may put the patients and the gynecologist in a great argument. The authors included 102 patients in the current study aiming to find an ideal contraceptive method during the chemotherapy cycles. The Society of Family Planning has issued guidelines about the contraceptive choices for women diagnosed with cancer. Although chemotherapy and radiation therapy can compromise fertility, many women remain fertile and pregnancy cannot be ruled out, even with patients with a severely compromised ovarian reserve (17).

It is well known that cancer increases the risk for thromboembolic disorders, therefore, estrogen/progestin contraception is not recommended during cancer treatment. World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend that women with active cancer or who have been treated for cancer in the last 6 months should avoid combined hormonal contraceptive methods (18). Hormones are known to play a role in the development of breast cancer; consequently, the use of combined contraceptive pills or progestin-only pills is not recommended in women undergoing treatment for breast cancer (10).

Furthermore, some reported that in breast cancer survivors, non-hormonal contraceptive methods should be used as first-line options. Hence, in the current study, authors randomly selected whether copper IUD or male condom method and did not refer to any hormonal contraception. The Copper IUD is considered as a hormone-free, long-acting reversible contraceptive and has no restrictions for use in the setting of current breast cancer(11).

Two common expected problems can meet patients receiving chemotherapy and IUD users. As they usually suffer from a state of immune compromisation with different forms of bone marrow suppression (19) including anemia, leucopenia and thrombocytopenia, there is associated increased risk of recurrent infection and higher tendency of bleeding. In the current study, the results support this as patients' examination after the first three months revealed that 21 out of 51 patients using IUD reported heavy cycles with significant increase in cycle duration meanwhile this may be attributed to the recent location of IUD and the associated hematological disorders occurred with the initiation of chemotherapy. Lower genital tract infections occurred

in 23 cases and upper genital tract infections were found in 8 cases that may be explained by the state of immune suppression and bone marrow affection as well as the endometrial congestion due to device location. Moreover after another 3 months (i.e. 6 months of starting chemotherapy), the above mentioned figures showed significant changes between both studied groups regarding the increase in the duration and the amount of menstrual bleeding in group (A) patients; lower genital tract infections increased to affect 29 patients, meanwhile upper genital tract infections remained unchanged (8 cases). This could be explained again by more immune compromise, thrombocytopenia and long standing endometrial congestion.

Barrier methods as male or female condoms are always considered as the convenient health hazards free methods of contraception but with a relatively high failure rate (14). In the current study, it was found that most of patients' partners were not satisfied with this method that reflects the sexual behavior of eastern couples. After explanation of benefits and risks, most of the couples agreed to continue the same method throughout the chemotherapy treatment cycles.

On the other hand condom users developed lower rates of genital tract infections and less cycle pattern disturbances compared to IUD users while in both groups, failure rates were zero and this was not surprising to the authors as it might reflect the relative less fertile anovulatory cycles present during chemotherapy.

Levonorgestrel Intrauterine system (LNG-IUS) was described by some studies (11) as an alternative method for contraception carrying the benefit of minimal bleeding and least failure rate, depending on the minimal systemic absorption of progesterone, especially in patients receiving tamoxifen that may induce endometrial hyperplasia. A large recent study conducted in Finland (20) found that the Finnish women who used the LNG-IUS for 5 years had an increased rate of breast cancer compared to the general Finnish population.

Tubal sterilization, and in some cases ovariectomy are sometimes used as an irreversible optimum method of contraception in cancer survivors (11). As a large group of patients with breast cancer diagnosed in their reproductive ages exhibited low parity, didn't complete their families yet, and they always seek for a reversible contraceptive method. Included patients in the current study were randomized for IUDs and barrier methods only.

Despite some recent studies recommend the use of copper IUD, as a highly effective, hormone-free method for women with a history of breast cancer or LNG-IUS to minimize menstrual blood loss in cases with anemia (21) the current study prefers the use of barrier methods (male condom for example) that showed a

high efficacy in maintaining less frequent cycles with less bleeding and low incidence of genital tract infections (p value <0.001) specifically while the patients were receiving chemotherapy.

Lastly the authors can state that; all women seeking contraception during the cancer treatment period should be provided with information about relative effectiveness of available contraceptives with their health hazards during such different period of treatment.

Conclusion

Despite the non-hormonal intrauterine contraceptive device was considered a safe effective method of contraception in the middle aged women with breast cancer on chemotherapy, barrier methods (male condom) with the precise use is recommended at least during the early critical post-operative period.

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