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Study Protocol

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Multidisciplinary Shared Decision Making for Fertility Preservation in Young Women With Breast Cancer

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ABSTRACT

Purpose: Fertility preservation (FP) is an important issue for young survivors of breast cancer. Although international guidelines recommend pre-treatment fertility counseling for women with breast cancer, there is no standardized protocol or referral system for FP in South Korea. There are also barriers to discussing FP that make patient-centered decision making difficult. This study aimed to develop a shared decision making program for FP and compare the rates of FP procedures between the usual care and shared decision making groups. We hypothesized that multidisciplinary shared decision making for FP would increase the rate of FP procedures and patient satisfaction.

Methods: The multidisciplinary shared decision making for FP in young women with breast cancer (MYBC) is a multicenter, clustered, stepped-wedge, randomized trial. A total of 1100 patients with breast cancer, aged 19–40 years, from nine hospitals in South Korea, will be enrolled. They will be randomized at the institutional level and assigned to usual care and shared decision making groups. Four institutions, each of which can recruit more than 200

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Conflict of Interest
The authors declare that they have no competing interests.

Data Availability
In accordance with the ICMJE data sharing policy, the authors have agreed to make the data available upon request.

Author Contributions
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patients, will each become a cluster, whereas five institutions, each of which can recruit more than 50 patients, will become one cluster, for a total of five clusters. The shared decision making groups will receive multidisciplinary programs for FP developed by the investigator. The primary outcome is the rate of FP procedures; secondary outcomes include fertility results, satisfaction, and quality of life. Outcomes will be measured at enrollment, treatment initiation, and the 1-, 3-, and 5-year follow-ups after starting breast cancer treatment.
Discussion: A multidisciplinary shared decision making program for FP is expected to increase fertility rates and satisfaction among young patients with breast cancer. This study will provide the evidence to implement a multidisciplinary system for patients with breast cancer.

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Keywords: Breast Neoplasms; Decision Making, Shared; Fertility; Fertility Preservation

INTRODUCTION

Breast cancer is the most common type of cancer in women of reproductive age; approximately 6% of patients newly diagnosed with breast cancer are under 40 years old [1]. Although the incidence of breast cancer in women over 40 years has decreased since 2000, the incidence of breast cancer in young women has remained stable for the past 30 years [2]. Young patients with breast cancer suffer from more biologically aggressive tumors, which are more commonly diagnosed at an advanced stage than those in older patients, and often have worse prognoses [3]. Young patients with breast cancer tend to receive intensive treatment, such as cytotoxic chemotherapy or long-term endocrine treatment for up to 10 years, resulting in temporary or permanent menopause. Accordingly, survivors of breast cancer experience the lowest fertility rate following the disease, with a 70% lower fertility rate than that of survivors of general cancer [4]. Some studies have found that more than half of the women of reproductive age diagnosed with breast cancer are concerned about infertility [5,6], which leads to a lower quality of life for survivors of breast cancer [7]. Therefore, fertility discussion and preservation are important issues to consider before treating young patients with breast cancer.

Several international guidelines recommend that young women be advised to undergo fertility counseling before starting breast cancer treatment [8,9]. All patients interested in fertility preservation (FP) should immediately be referred to an appropriate fertility specialist. However, there is an unmet need for fertility-related information for young patients with breast cancer [5,10]. The rates of referral to a reproductive specialist for FP also remain low [11,12]. Additionally, young patients with cancer face serious decisional conflicts regarding FP when diagnosed with cancer [13]. Decision making regarding FP is a complex process with many patient-dependent factors. Therefore, there is an increasing need for shared decision making with patient involvement. Shared decision making has been defined as an approach in which clinicians and patients share the best available evidence, and patients are supported in considering options for achieving informed preferences [14]. Decision aids are also developed to assist in treatment decision making and reduce decisional conflicts. Some decision aids for FP in women with breast cancer have been developed and their efficacy demonstrated [15-17], most of which are from Western countries; Asian studies are scarce [18].

In South Korea, the annual number of newly diagnosed patients with breast cancer rose from 6,234 in 2000 to 28,049 in 2018, representing a more than four-fold increase [19]. In

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contrast to Western countries where the incidence of breast cancer increases with age [1], a characteristic feature of breast cancer in Korea is that women between the ages of 40 and 49 years experience the highest incidence of breast cancer [19]. Therefore, the proportion of premenopausal women with breast cancer in South Korea is higher than in Western countries. However, there are barriers to the education about and discussion of FP due to time constraints in clinics and the lack of a multidisciplinary system [20], making patient-centered, shared decision making difficult. Although FP consultations are conducted in each hospital unit, there is no standardized protocol or referral system for FP in South Korea. In this situation, the development of a shared decision making program and standardized system for FP is an important challenge. Therefore, we have developed a multicenter, stepped-wedge cluster randomized trial for multidisciplinary shared decision making for FP in young women with breast cancer (MYBC) and will evaluate the effect of the shared decision making program.

The primary aim of this study is to develop multidisciplinary shared decision making FP programs and compare the rates of FP procedures between usual care and shared decision making groups. The secondary aims are to compare fertility-related outcomes between the two groups, including the rates of pregnancy attempts and success, the number of retrieved oocytes and embryos from FP procedures, ovarian function, depression, anxiety, insomnia, quality of life, and satisfaction. We will also compare disease-free survival (DFS) and overall survival (OS) between patients who underwent the FP procedure and those who did not.

METHODS

Study design

The MYBC study is a multicenter, clustered, stepped-wedge, randomized trial. Patients will be recruited from nine academic medical centers in South Korea. This study design allows a random sequential introduction of the intervention to clusters, from control (usual care) to intervention (shared decision making). Therefore, the intervention will be implemented at randomized time steps, in which one cluster changes from the control to the intervention condition until each cluster has implemented the shared decision making program for FP. The usual care group will follow each institution's usual processes, whereas the shared decision making group will receive multidisciplinary FP programs developed by the investigator before treatment. The stepped-wedge cluster study design is shown in **Figure 1**. Additionally, this study will retrospectively review the retrospective control group of patients with the same inclusion criteria.

Randomization

Randomization will be performed at the cluster level. Nine academic medical centers will participate in this study. Of these centers, four institutions, each capable of recruiting more than 200 patients, will be considered as individual clusters, whereas five institutions, each capable of recruiting more than 50 patients, will be considered as one cluster, yielding a total of five clusters. Randomization will be stratified by hospital volume and the presence of multidisciplinary clinics. To optimize the balance between the groups, the step of transition to the intervention group will be randomly allocated with a 2:1:2 allocation ratio in three steps. Due to the sequential introduction of the intervention in this study, blinding participants and researchers to group allocation is not possible.

Cluster	Period 1	Period 2	Period 3	Period 4
Cluster 1	55	55	55	55
Cluster 2	55	55	55	55
Cluster 3	55	55	55	55
Cluster 4	55	55	55	55
Cluster 5	55	55	55	55

Expected number of new recruits in each cluster and period

Control	275	165	110		n = 550
Intervention		110	165	275	n = 550
Total	275	275	275	275	n = 1,100

Figure 1. Stepped-wedge cluster design.

Study population

The MYBC study enrolls premenopausal women with breast cancer stages 0–III, aged 19–40 years at diagnosis, regardless of their marital status. Premenopausal status was defined as a menstruation history in 1 year. Eligible patients should have an Eastern Cooperative Oncology Group performance status of 0–2. We will exclude the following patients: those who have received chemotherapy, radiotherapy, endocrine and target therapies, or surgery for breast cancer before enrollment; those who have been diagnosed with primary malignancies at other sites before enrollment; those who are pregnant at the time of enrollment; those who cannot understand the study; and those who are not available for follow-up after the initial treatment. The retrospective control group is subject to the same inclusion and exclusion criteria.

Endpoints and assessments

The primary endpoint is the comparison of the rates of FP procedures between the usual care and shared decision making groups. During the 5-year study period, the following FP procedures will be attempted: oocyte, embryo, and/or ovarian tissue cryopreservation, and gonadotropin-releasing hormone agonist therapy. Institutions that perform FP are unrestricted. In cases where FP is performed at participating institutions, the presence and method of FP will be verified using medical records. When the FP is implemented at a hospital that is not a participating institution, the researcher will review the relevant patient information collected during the study visits. The secondary endpoints are the comparison of the following between the two groups: (1) the number of retrieved oocytes and embryos, (2) the rates of pregnancy attempts and success, (3) patient and spouse satisfaction, (4) ovarian function, and (5) depression, anxiety, insomnia, and quality of life. Additionally, we will investigate the treatment delay period for FP and the differences in DFS and OS between patients who underwent the FP procedure and those who did not. If a patient currently has a spouse, the spouse will also receive a questionnaire, and satisfaction with decision making will be assessed. Furthermore, we will collect data on FP procedures, fertility counseling, parity, and survival of the retrospective control group, and compare the rates of FP procedures and pregnancy success between the retrospective and prospective groups.

Shared decision making program development

A shared decision making program will be developed at the beginning of the study. Principal investigators, psychiatrists, patient advocates, the Korean Society for Fertility Preservation, and the Korean Academy on Communication in Healthcare comprise the task force team for program development. The team will develop and share the program with all participating institutions. Leaflets, patient education videos, a website, and a list of institutions capable of performing FP will be developed for the shared decision making program.

Patient questionnaires

The survey items of the baseline questionnaires were derived from the previous Helping Ourselves, Helping Others (HOHO)—the Young Women's Breast Cancer Study (NCT01468246), a North American multicenter prospective cohort study—and modified by the investigators. In addition, the patients' quality of life will be measured based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 and Quality of Life Questionnaire Breast Cancer-23. Menopausal symptoms will be evaluated using the Menopause Rating Scale. Patient levels of depression, anxiety, and insomnia will be measured using the Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, Insomnia Severity Index, and Cancer-related Dysfunctional Beliefs about Sleep. Marital satisfaction will be measured using the revised Kansas Marital Satisfaction Scale (KMSS). Patients will complete the International Physical Activity Questionnaire to evaluate their physical activity. Conflicts and regrets in the FP-related decision process will be examined using the Decisional Conflict Scale and the Decisional Regret Scale. The measures and time of assessment for the prospective groups are shown in **Figure 2**, in the format recommended by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. Questionnaires will be administered at enrollment, at the start of treatment, and at the 1-, 3-, and 5-year follow-ups after the initiation of breast cancer treatment. Patients will be followed for up to 5 years after starting treatment for breast cancer. The SPIRIT checklist is provided in **Supplementary Table 1**.

Spouse questionnaires

The survey items in the questionnaires for patients' spouses include the spouses' sociodemographic information, fertility concerns, and satisfaction with the FP process (information, counseling, and procedures), and were developed by the investigator. Spousal marital satisfaction will be measured using the revised KMSS. Spouses will complete the Multidimensional Scale of Perceived Social Support to measure social support, the Post-Traumatic Growth Inventory to evaluate internal growth, and the caregiver reaction assessment to assess the caregiving experience. The survey timeline for spouses is shown in **Supplementary Figure 1**.

Patient advocate and community

The MYBC study has secured a patient advocate to review the study progress, receive feedback, and develop the multidisciplinary program for FP with the investigators. Additionally, the MYBC web community will be available to the study participants. The investigators' live-streaming lectures will be broadcast at least once a month. Real-time communication with patients and clinicians will be achieved through chats during broadcasts.

Sample size calculation

It has been reported that the difference in the choice of the FP procedure before and after the FP education program increased from 2% to 12% [21]. Based on these results, it was assumed

		Study period					
		Enrollment & allocation	Post-allocation				Close-out
Timepoint		Before counselling	FP visit (optional)	Treatment start	1-year	3-year	5-year
	Enrolment:						
	Eligibility screen	X					
	Informed consent	X					
	Interventions:						
	Usual care group						
	Shared decision-making group	←	→				
	Assessments:						
Baseline assessment	Demographics	X					
	Obstetrics and gynecologic-related information	X		X	X	X	X
	Vital sign, height, weight and BMI	X		X	X	X	X
	Breast cancer-related information	X			X		
	Follow-up of breast cancer				X	X	X
	Medical history	X	X	X	X	X	X
Fertility assessment	Laboratory tests (FSH, E2, AMH, Vit D level)	X		X	X	X	X
	Knowledge of FP assessment	X	X	X			
	Selection and method of FP procedures	X	X	X	X	X	X
	Attempt to conceive and childbirth history				X	X	X
Baseline questionnaires	Background	X			X	X	X
	Breast cancer diagnosis	X					
	Family history				X		X
	Health habit	X			X	X	X
	Gynecologic and fertility history	X			X	X	X
	Concerns about infertility	X	X		X	X	X
	Religion and spirituality	X					
	Breast cancer treatment and decision making				X		X
	Satisfaction for counselling		X	X	X	X	X
	Satisfaction for FP procedures			X	X	X	X
Additional questionnaires	PHQ-9	X			X	X	X
	GAD-7	X			X	X	X
	ISI + C-DBS	X			X	X	X
	Revised KMSS	X			X	X	X
	IPAQ	X			X	X	X
	EORTC QLQ C-30	X			X	X	X
	EORTC QLQ BR-30	X			X	X	X
	MRS	X			X	X	X
	Decisional regret scale		X	X	X	X	X
	Decisional conflict scale		X	X	X	X	X

Figure 2. Timeline for enrollment and assessment of the prospective group.
FP = fertility preservation; BMI = body mass index; FSH = follicle-stimulating hormone; AMH = anti-Mullerian hormone; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; ISI = Insomnia Severity Index; C-DBS = Cancer-Related Dysfunctional Beliefs about Sleep; KMSS = Kansas Marital Satisfaction Scale; IPAQ = International Physical Activity Questionnaire; EORTC = European Organisation for Research and Treatment of Cancer; QLQ C-30 = Quality of Life Questionnaire Core-30; QLQ BR-23 = Quality of Life Questionnaire Breast Cancer-23; MRS = Menopause Rating Scale.

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that the median value of 5% before and after the education program was due to general education. Therefore, the 12% after the shared decision making program was assumed to represent an improvement of 7% in the choice of the FP procedure.

To achieve a power of 0.80 at a significance level of 0.05, assuming five clusters, four periods, and three steps, an average of 49 patients per period in a cluster is required. Considering a dropout rate of 10%, 55 patients per period per cluster, 550 patients per group, and a total of 1,100 patients are required for this study. The intracluster correlation coefficient, interpreted as the correlation between any two observations in the same cluster, is set to 0.050. The required sample size was calculated using PASS 15 Power Analysis and Sample Size Software (NCSS, LLC., Kaysville, USA).

For the retrospective control group, 10-year data from nine hospitals will be retrospectively collected, and data from at least 3,000 patients aged 19–40 are expected to be collected.

Data collection and confidentiality

All data will be collected via the electronic case report form (CRF) and electronic questionnaires. These data will be stored in a password-accessible database that is only accessible to the investigators. Patient data will be stored as the screening and allocation numbers given by the CRF, which will be used as study participant identifiers. All data will be deleted 3 years after the end of the study.

Data monitoring

The monitoring committee is chaired by the principal investigator, and is composed of a statistician and a member of the academic research office of Asan Medical Center. The committee evaluates the data and safety monitoring of the study. Multicenter data monitoring will be conducted by an external contract research organization.

Data analysis

Data will be analyzed following the intention-to-treat principle, including protocol deviators. A per-protocol analysis will also be performed as a secondary analysis. Intention-to-treat analysis refers to the data analysis of participants who receive an enrollment number and complete at least one questionnaire assessment. A per-protocol analysis analyzes the data collected from participants who complete the clinical study protocol among the participants included in the full analysis set. A missing value is imputed as the participant's previously observed value.

Primary outcomes will be described using the chi-square test or Fisher's exact test. The frequency and percentage of the selection of FP procedures will be presented, and a generalized estimating equation that considers random effects (cluster) and fixed effects (period and group) will be used to draw a comparison between the usual care and shared decision making groups. In the case of secondary outcomes, continuous variables will be summarized using descriptive statistics (mean, median, minimum, maximum, and standard deviation) and for the amount of change at each visit compared to the baseline. A linear mixed model will be used to compare the two groups, considering clusters as random effects and periods as fixed effects. Additionally, for time comparison within groups, a linear mixed model with the interaction between group and time will be used. For categorical variables, descriptive statistics (frequency and percentage) will be used, and the two groups will be compared using the chi-square test or Fisher's exact test. Descriptive statistics (mean and standard deviation) will be used for continuous variables, and the two groups will be

compared using an independent *t*-test or Wilcoxon rank-sum test. The Kaplan–Meier method will be used to estimate the DFS and OS rates and generate survival curves. The log-rank test will be used to evaluate the univariate analysis of the significance of the differences between survival rates. A subgroup analysis will be performed according to patient age. *p*-values < 0.05 will be considered statistically significant. All statistical analyses will be performed using SPSS version 21.0 (IBM Corp., Armonk, USA) and SAS version 9.4 (SAS Institute, Cary, USA).

Ethics and dissemination

This study (protocol version 3.0, January 28, 2022) has been approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB approval No. 2021-1382). Written informed consent will be obtained from all participants before they complete the survey. Protocol modifications since the one currently written will be decided upon by all investigators through online and offline meetings and updated in the trial registry after approval by the IRB. The study results will be shared through conference presentations and publications in peer-reviewed journals.

Safety considerations

There are no safety issues when applying multidisciplinary FP programs.

Trial status

This study is registered at ClinicalTrials.gov (Identifier: NCT05139641). The expected time for recruitment in each period was six months. The recruitment of the prospective groups began on January 18, 2022, and a total of 122 patients were enrolled by July 22, 2022. Medical chart reviews of retrospective control groups of participating centers are in progress.

DISCUSSION

Young women with breast cancer should be well informed about and have a desire to discuss the impact of adjuvant therapy on fertility and menopausal status [10]. Our previous study reported that young patients with breast cancer were not well informed about the side effects of anticancer therapy on ovarian function and fertility, and that their knowledge improved after education [21]. Therefore, it is important to provide patients with information on fertility to make informed choices. Additionally, some studies have revealed that early referral to reproductive specialists provides many benefits to patients. Late referrals are more likely to experience decision conflicts than early referrals (odds ratio, 4.8; 95% confidence interval, 1.5–21.6) [22]. Early referral before breast surgery also allows women with breast cancer to receive ovarian stimulation and start chemotherapy earlier than those who are referred after surgery. Patients who are referred before surgery can use this additional time to undergo multiple cryopreservation cycles and preserve a higher number of oocytes and embryos [23]. Therefore, it is necessary to help women make informed decisions regarding FP and establish a system through which patients who want to preserve their fertility can be referred to reproductive specialists in a timely manner. However, a well-equipped and appropriate system is lacking in many hospitals, and an individual approach is often used.

Young breast cancer cohorts have been established in Western countries—HOHO, Young and Strong, and the PREgnancy and FERtility—while studies related to their fertility have been actively conducted [24,25]. Current trials on FP in young patients with breast cancer are mainly prospective cohort studies. Thus, it is difficult to focus on the importance of the shared decision making process and its effects. We designed this study to develop a shared

decision making program and evaluate its effects on patient satisfaction. Additionally, we include the partners of survivors of cancer by conducting a survey of the patients' spouses. The benefits of patient advocates in clinical trials have been previously reported [26,27]. The MYBC study involves a patient advocate who is engaged throughout the study from the planning stage. Additionally, the study created a web community that provides the investigators' live-streaming lectures and monthly real-time communication between enrolled patients and clinicians. These will lead to patient-centered research.

Regarding the study design, the distance between hospitals in South Korea is not as great as that in Western countries, and the patient internet community is active. Information regarding current clinical trials can be easily shared among patients with breast cancer. Consequently, it is difficult to conduct a parallel-cluster randomized trial, and there is a potential for contamination across groups. In addition, there was an ethical problem associated with patient assignment to the control group. Therefore, we adopted a stepped-wedge, cluster randomized trial design, in which there was an initial period of no exposure to interventions prior to program development, and all interventions were present in each cluster after program development. Additionally, a retrospective control group was established to correct for biases, such as the prospective control group's increased interest in FP and improved counseling activity after enrollment.

Currently, information on patients' FP is insufficient, and some patients are unaware of FP before breast cancer treatment. Through the MYBC study, sufficient discussion with patients is expected to increase their knowledge of FP and their satisfaction. Patients are also expected to achieve a better quality of life and better survival rates if an integrated treatment plan for breast cancer treatment and FP is established at the time of breast cancer diagnosis. If a multidisciplinary shared decision making program is effective, it can be implemented as a part of routine care to help with decisions regarding FP in patients of reproductive age with breast cancer. The MYBC study will provide the evidence required to establish a multidisciplinary system for FP in young patients with breast cancer in South Korea.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

The Standard Protocol Items: Recommendations for Interventional Trials checklists

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Supplementary Figure 1

Timeline of the assessment of spouses in the prospective group.

Click here to view

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