Do Patient Characteristics Decide if Young Adult Cancer Patients Undergo Fertility Preservation?

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Purpose: The Fertility Attitudes and Cancer Treatment Study (FACTS) is a two-phase research initiative aimed to understand factors involved with decision making for future fertility. The FACTS will improve services and utilization of fertility preservation (FP) before cancer treatment. Phase-I examined patient characteristics as associated with FP decision.

Methods: A retrospective cohort study of 108 reproductive-aged (18–45 years) males and females who received a fertility consultation before cancer treatment from January 1, 2012 to April 30, 2014 was conducted. Chi-square, student's *t*-test, and logistic regression were conducted to examine associations with FP decision.

Results: The utilization rate of FP following fertility consultation was 49%. Gender was the most significant factor contributing to FP decision; 74% of those who choose FP were male (odds ratio = 12.5; 95% confidence interval 5.1–31.4). Those who opted for FP were more likely to be Caucasian ($p=0.042$), have a solid tumor ($p=0.03$), and have a shorter time from diagnosis to fertility consultation (29.5 vs. 58.8 days; $p=0.017$). Age, relationship, tumor location, treatment plan, and parity were not significant predictors of FP.

Conclusions: Current perceptions about patient demographics do not predict FP utilization by young adult cancer patients. Providing patients an informed fertility consultation has demonstrated an increase in FP utilization to nearly one-half of patients. Despite gender being a significant factor in choosing FP, the study did not provide reasons as to why. The phase-II study will explore patients' reasons for FP decision in a qualitative design to understand these differences.

Keywords: fertility decision-making, fertility preservation, fertility preservation barriers, fertility preservation utilization, oncofertility

Introduction

THE AMERICAN CANCER Society has estimated that approximately 140,000 men and women under the age of 45 will be diagnosed with cancer each year.¹ Today there are a variety of treatment options for cancer diagnoses, which contribute to longer and more productive lives by survivors.² However, challenges still remain for cancer survivors striving to return to normalcy. One significant concern among young survivors is their ability to have children after aggressive cancer therapies.^{3–6} With young survivors reporting psychosocial effects and a loss to their quality of life related to infertility, there is a critical need for providing effective fertility preservation (FP) services to cancer patients.

Previous studies provide a rich understanding of some of the challenges to adequately providing fertility information. These challenges include the urgency to initiate treatment,

inadequate information provided to patients, clinic time constraints, cost, and perceptions around patients' gender, age, parity, race, and relationship status.^{7–19} Additionally, survivorship studies have identified some of the patient barriers to utilizing FP, including a lack of sufficient knowledge, access to care, and sociodemographic status.^{7,8,15,20–23} Few studies have identified patients at the time of treatment decision to best understand potential predictors for FP treatment decisions.

The Fertility Attitudes and Cancer Treatment Study (FACTS) is a two-phase research initiative aimed to improve our understanding of the complex factors involved with patient decisions regarding future fertility. Typically, oncology patients are expected to make critical decisions with limited information about reproductive risks and are often urged to initiate cancer treatment immediately. Patients are left uninformed of fertility risks and their desires for future fertility

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are inadvertently neglected.^{24,25} The quality of care for these patients can be improved with informed decision making.^{5,26,27} Phase-I, a retrospective study of clinic patients, aimed to measure FP utilization rates and identify potential characteristics associated with treatment. These findings will inform a phase-II qualitative interview study. The findings of the FACTS will be used to contribute toward improving services and utilization of FP before cancer treatment.

The FACTS examined patients who received a fertility consultation before cancer treatment to fully understand considerations for future fertility. Much of our understanding in this area relies on retrospective studies of survivors exploring patient's desires only after completing cancer treatment.^{3,4,6,20,24,28,29} These past studies identified psychological reactions and suggest informational needs, but provide little data regarding patient factors that drive decision. Once some of the current system challenges are removed with informed fertility consult (access to care, knowledge deficits), true barriers, or patient factors, to utilizing FP can be identified. The authors hypothesized that gender would be the most significant factor contributing to FP decisions. Based on previous studies, the authors also hypothesized that age, race, relationship status, parity and cancer type will be associated with FP treatment decision.^{7,8,15,16,18,19,30–33}

Methods

An Oncofertility program was formally introduced at the University of Colorado Denver in January 2012. Providers are alerted through the electronic medical records system at the close of each new oncology consult for a young adult that the patient is recommended to be referred to Oncofertility services. The patients referred to the Oncofertility program represent a population of cancer patients interested in information regarding reproductive health risks. Approximately, 10% of newly diagnosed adolescents and young adults (AYA) are currently referred to the Oncofertility program at onset of diagnosis at our institution. A retrospective cohort study was conducted by chart review to identify potential predictors for FP treatment among AYA oncology patients. The study population included all reproductive-aged (18–45 years) males and females who received a fertility consultation through the Oncofertility program at the University of Colorado Denver from January 1, 2012 to April 30, 2014. The Oncofertility program saw 260 patients during this interval. Only patients with a new diagnosis of cancer were included in the cohort study, representing 42% of all Oncofertility consultations. Participants included a wide variety of cancer types and were not excluded based on a specific cancer diagnosis or stage.

Survivor studies have reported utilization rates for FP ranging from 4% to 43%.^{7,18,30,32} Based on these utilization rates, we used the median to hypothesize current utilization rates at 24%. Using the current prevalence rate of 0.24, we then calculated an Asymptotic Wald interval to estimate a 95% confidence interval (95% CI) for the current utilization rate ranging from 0.147 to 0.324 and a sample size of at least 72 persons to obtain less than a 5% margin of error.

A total of 108 patient records were identified for participation in this study (Power=0.91). A waiver of consent and HIPAA authorization was obtained for all participants of this study. Demographic and clinical outcomes were obtained retrospectively from the Oncofertility patient registry and

verified against the patient's medical record. Any missing data was either obtained through the patient's medical record or by contacting the patient if appropriate consent for contact was on file. Variables collected included gender, age, race/ethnicity, insurance status, educational level, relationship status, parity, sexual activity, FP decision, cancer diagnosis, FP and cancer treatments, and clinical dates for FP and cancer treatment. Additional data with regard to reasons for FP decision was abstracted from the clinician visit notes. A time to consult (TTC) variable was created using the date of FP consult minus date of diagnosis, measured in days. A time to treatment was created using the date initiated cancer treatment minus the date of FP consult, measured in days.

Statistical analysis

This study assessed a population of newly diagnosed cancer patients, males and females, who received a fertility consultation. De-identified data was exported into SPSS 22.0 for data analysis. The null hypothesis stated that each independent variable was not associated with the primary outcome FP decision (elected FP versus not following consultation). Bivariate analysis was conducted with a 95% CI and an alpha level of 0.05, to determine significant associations between each independent variable and FP decision. For categorical variables, a Chi-square analysis was performed. Instances where a particular variable had observations with $n < 5$, a Fisher's exact test was used. Continuous or linear variables were analyzed using a two-sample *t*-test. Multivariable analysis was conducted with a logistic regression model to determine independent associations with FP decision.

Results

The study population included 108 AYA newly diagnosed cancer patients, in which 55% were female ($n=59$). At the time of publication, there was a >95% survival rate of participants with four patients deceased within an average of 293 days from the time of diagnosis; only one of the deceased patients opted to undergo FP at the time of diagnosis. The utilization rate of FP following fertility consultation in this study population was 49% (80% in males, 24% in females).

Gender was found to be the most significant factor in whether patients opted for FP or not; among those who chose FP, 74% were males (odds ratio [OR]=12.5; 95% CI 5.1–31.4). Among males, race and tumor type were significant factors in predicting FP decision; after logistic regression only tumor type remained as a significant predictor for FP decision. Among males who elected FP, they were 16.3 times more likely to have a solid tumor versus a blood cancer (adjusted OR 16.3; 95% CI 1.5–180.0). Among females alone there were no significant associations among study characteristics and FP decision.

Minorities represented 19% of the study population. Those who opted for FP were 3.3 times (95% CI 1.1–9.9; $p=0.042$) more likely to be Caucasian versus being Hispanic or another minority, when compared with those not choosing FP. Healthcare insurance type was not significant in predicting FP decision. Nearly one-fourth of the study population had federal or state medical insurance assistance (Medicaid or Colorado Indigent Care Program), however, these patients made similar decisions about FP as those with private insurance. Age was not identified as a significant factor in FP

decision. Age was normally distributed in the study population with the mean age of patients 29.5 ± 6.4 years. Education level, relationship status, parity, and sexual activity were also similar between those choosing FP and those not. Table 1 demonstrates the distribution of the study demographic and treatment characteristics. Table 2 shows the unadjusted odds ratio for factors associated with FP.

The study population included patients of a wide variety of malignancy. The majority of patients represented those with solid tumors (92%). Tumor type was significant with FP decision; those choosing FP were more likely to have a solid tumor versus a blood cancer (98% vs. 2%, $p=0.03$). Cancer diagnosis of reproductive versus nonreproductive origin was not a predictor for FP decision. Additionally, cancer treatment plan (surgery, chemotherapy, radiation, and/or transplant) was not associated with FP decision. Gender, race, and tumor type were all confirmed to be independent factors for FP decision using logistic regression.

TTC was found to be a significant factor in patients' FP decision making, with shorter TTC attributing to choosing FP. Among those who choose FP, there was an average of 29.5 days from the time of diagnosis to consult compared with 58.8 days for those who did not choose FP. Furthermore, TTC was found to be an independent predictor for FP when examined using logistic regression.

Patients who elected FP

Nearly 50% of the study population opted for one of the following FP options: sperm cryopreservation, embryo preservation, or oocyte preservation. An additional 16 participants desired FP, but were considered poor candidates for FP after fertility consult. One-half of these 16 patients initiated the FP process with a fertility workup, involving a semen analysis or biomarkers for ovarian reserve, to determine baseline fertility parameters. Among those who ultimately underwent FP, 49 had successful cycles (3 excluded because they underwent FP after initiating cancer treatment, 1 excluded because FP treatment was at another facility and results are unknown). The mean age of those with successful FP was 28.9 years. For women undergoing oocyte or embryo banking, the mean number of days of stimulation was 9.4 (6.0–11.0) days. Females undergoing FP started cancer treatment on average 41.3 days from the time of diagnosis. Males undergoing FP initiated cancer treatment on average 8.5 days from the time of diagnosis.

Patients who did not elect FP

Among those who did not elect FP ($n=55$), 40.0% did not choose FP due to patient factors that included: completed family, primary concern was cancer treatment, concern for genetic abnormalities or use of hormones, and religious reservations. Twenty-nine percent were considered poor candidates for FP following a fertility assessment due to initiation of cancer treatment and female age. One patient was pregnant at the time of FP consult and, therefore, was not eligible to undergo FP. Only 12.7% of patients cited finances as a reason for not undergoing FP in this study. Additional reasons for not undergoing FP included low risk of impaired fertility (9.1%), oncologist urged patients to not delay treatment (7.3%), and patients were interested in hormonal management only (1.8%).

TABLE 1. DEMOGRAPHIC AND TREATMENT CHARACTERISTICS OF 108 ADOLESCENTS AND YOUNG ADULTS ONCOFERTILITY PATIENTS SEEN AT THE UNIVERSITY OF COLORADO DENVER FROM JANUARY 1, 2012 to APRIL 20, 2014

Characteristics	Yes FP (n = 53), mean $\pm$ SD or N (%)	No FP (n = 55), mean $\pm$ SD or N (%)
Age, years	29.19 $\pm$ 6.15	30.7 $\pm$ 6.55
Gender		
Male	39 (73.6)	10 (18.2)
Female	14 (26.4)	45 (81.8)
Race/ethnicity		
Caucasian	48 (90.6)	41 (74.5)
Hispanic/other minority	5 (9.4)	14 (25.5)
Relationship status		
In a relationship	31 (58.5)	35 (63.6)
Single	22 (41.5)	20 (36.4)
Insurance status		
Government assisted	11 (20.8)	15 (27.3)
Military coverage	4 (7.5)	6 (10.9)
Self-pay	1 (1.9)	1 (1.8)
Private insurance	37 (69.8)	33 (60)
Education		
Less than college grad	21 (42)	19 (38)
College grad or more	29 (58)	31 (62)
Parity (previous children)		
None	46 (86.8)	42 (76.4)
One or more	7 (13.2)	13 (23.6)
Sexually active		
Yes	35 (67.3)	38 (74.5)
No	17 (32.7)	13 (25.5)
Cancer type (reproductive system cancers vs. none) ^a		
Endocrine	9 (17)	18 (32.7)
Pelvic tumors	17 (31.1)	16 (29.1)
Non-reproductive	27 (50.9)	21 (38.2)
Tumor type ^b		
Solid	52 (98.1)	47 (85.5)
Blood	1 (1.9)	8 (14.5)
Treatment plan includes surgery		
Yes	41 (77.4)	35 (63.6)
No	12 (22.6)	20 (36.4)
Treatment plan includes chemotherapy		
Yes	47 (88.7)	45 (81.8)
No	6 (11.3)	10 (18.2)
Treatment plan includes radiation		
Yes	23 (43.4)	26 (47.3)
No	29 (58)	31 (62)
Treatment plan includes bone marrow or stem cell transplant		
Yes	2 (38)	3 (5.5)
No	51 (96.2)	52 (94.5)
Time to consult, days	29.51 $\pm$ 34.55	58.82 $\pm$ 81.92
Time to treatment, days	20.63 $\pm$ 32.99	13.07 $\pm$ 12.47

^aEndocrine: breast, head and neck, pituitary, and thyroid diagnoses. Pelvic tumors: Colorectal, all gynecological, peritoneal, prostate and testicular diagnoses. Nonreproductive: all other.

^bSolid: brain, breast, all gynecological, gastrointestinal, germ cell tumors, head and neck, Hodgkin's lymphoma, melanoma, non-Hodgkin's lymphoma, pancreatic, peritoneal, all sarcomas, small cell tumors, and testicular diagnoses. Blood: acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, and other leukemia.

FP, fertility preservation; SD, standard deviation.

TABLE 2. CHI-SQUARE ANALYSIS OF FACTORS ASSOCIATED WITH FERTILITY PRESERVATION DECISION IN ADOLESCENTS AND YOUNG ADULTS ONCOFERTILITY PATIENTS

Factors	Odds ratio (95% CI)		
	All patients (N=108)	Males (n=49)	Females (n=59)
Age ^a	<i>p</i> = 0.220	<i>p</i> = 0.243	n/a
Gender			
Male	12.54 (5.07–31.39) ^b		
Female	1.0		
Race/ethnicity			
Caucasian	3.28 (1.09–9.88) ^b	5.83 (1.14–29.9) ^b	3.71 (0.43–31.95)
Hispanic/other minority	1.0	1.0	1.0
Relationship status			
In a relationship	0.81 (0.37–1.75)	0.63 (0.15–2.6)	3.31 (0.66–16.67)
Single	1.0	1.0	1.0
Insurance status			
Government assisted	0.65 (0.26–1.62)	1.00 (0.13–8.97)	0.19 (0.01–1.67)
Military coverage	0.60 (0.15–2.29)	0.20 (0.02–1.77)	0.81 (0.03–10.46)
Self-pay	0.89 (0.05–14.83)	—	—
Private insurance	1.0	1.0	1.0
Education			
Less than college grad	1.18 (0.53–2.63)	0.90 (0.15–5.22)	0.72 (0.19–2.70)
College grad or more	1.0	1.0	1.0
Parity (previous children)			
None	2.03 (0.74–5.58)	0.23 (0.03–2.10)	1.19 (0.24–6.53)
One or more	1.0	1.0	1.0
Sexually active			
Yes	0.70 (0.30–1.66)	0.70 (0.30–1.66)	4.88 (0.57–41.4)
Cancer type (reproductive system cancers vs. none) ^c			
Endocrine	0.39 (0.15–1.03)	—	3.11 (0.48–25.30)
Pelvic tumors	0.83 (0.34–2.01)	1.21 (0.22–7.18)	2.15 (0.26–20.80)
Nonreproductive	1.0	1.0	1.0
Tumor type ^d			
Solid	8.85 (1.07–73.44) ^b	16.29 (1.47–179.96) ^b	—
Blood	1.0	1.0	1.0
Treatment plan includes surgery			
Yes	1.95 (0.84–4.55)	2.90 (0.69–12.15)	3.0 (0.59–15.16)
Treatment plan includes chemotherapy			
Yes	1.74 (0.58–5.19)	1.33 (0.12–14.38)	0.92 (0.21–3.99)
Treatment plan includes radiation			
Yes	0.86 (0.40–1.83)	6.26 (0.72–54.41)	0.80 (0.24–2.66)
Time to consultation	<i>p</i> = 0.017 ^b	<i>p</i> = 0.233	<i>p</i> = 0.068

^aIndependent sample *t*-test used for analysis of continuous variable.

^bIndicates clinical significance.

^cEndocrine: breast, head and neck, pituitary, and thyroid diagnoses. Pelvic tumors: colorectal, all gynecological, peritoneal, prostate and testicular diagnoses. Nonreproductive: all other.

^dSolid: brain, breast, all gynecological, gastrointestinal, germ cell tumors, head and neck, Hodgkin's lymphoma, melanoma, non-Hodgkin's lymphoma, pancreatic, peritoneal, all sarcomas, small cell tumors, and testicular diagnoses. Blood: acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, and other leukemia.

95% CI, 95% confidence interval.

Discussion

Previous studies have found that only a quarter of AYA cancer patients undergo FP at the time of diagnosis. These studies have examined FP utilization rates retrospectively, and in most cases these patients report they did not receive adequate information about fertility risks and options to consider FP.^{7,18,30,32} FACTS included males and females all of whom were referred to Oncofertility services and received a fertility consult at the time of their initial cancer diagnosis. Our study found an increase in FP utilization to 49% of AYA cancer patients following an informed consultation, compared with the average of 24% utilization found in previous

studies in which patients did not necessarily get a referral to an Oncofertility specialist.^{7,18,30,32} The FACTS suggests that young cancer patients are more likely to undergo FP following a comprehensive fertility consultation.

A unique aspect of this study is the similar proportion of female and male patients included in a single study. With gender being the most significant difference as to whether an AYA cancer patient chooses FP, one would expect differences in male and female factors for FP decision. However, we found no clear gender differences in factors associated with FP utilization. In this study, we eliminated some of the system factors, such as referral and clinical time for discussion, as well as patient and clinical factors, such as sociodemographics and

disease status, as reasons for different FP rates for males and females. We hypothesize that the differences associated with choosing FP may be modifiable factors, such as cost, support, and patients' priorities. We identified some of these factors as potential barriers for those who did not elect FP. We plan to further study patient factors driving decision in a qualitative study, following this phase-I study.

Previous studies proposed that minorities and the underinsured do not have access to care for FP services.^{7,21} In this study of AYA cancer patients receiving fertility consult, insurance was not a factor influencing FP decision. In fact, 21% of those who underwent FP treatment had government-assisted healthcare (i.e., Medicaid), with no coverage for infertility or FP services. Often patients who are underinsured, or have government-assisted insurance, are not referred to assisted reproductive services because of their lack of healthcare coverage. However, in a clinical setting with an established Oncofertility program, patients were referred despite insurance coverage and the underinsured made decisions to elect FP similarly to the insured patients. While insurance did not contribute to FP decision, race (ethnicity) was identified as a factor in FP decision making. With all patients in the study having access to FP information and options, this suggests that there are alternative reasons for minorities to not undergo FP treatment. Phase-II will further examine cultural aspects and expectations for family to better understand these differences.

It is important to note the demographic characteristics that were not significant factors associated with FP decision. Age, education, relationship, and parity have all been recognized as possible influences for FP in the past.^{8,16,19,32,33} However, in our study population, they were not found to be significant factors contributing to FP decision.

Among clinical characteristics, both tumor type and TTC were factors associated with FP decision. Those who underwent FP were nearly nine times more likely to have a solid tumor versus a blood cancer diagnosis ($p=0.03$). This may suggest that those with solid tumor malignancies have improved health statuses and are better to undergo FP or have more time to consider options. These factors will be further explored in the qualitative study. TTC was also found to be significant. AYA patients who chose FP treatment had a significantly shorter time from diagnosis to receiving an FP consult as compared with those who did not elect FP treatment. As FP programs and referral systems are developed, TTC is an important element to streamline patient care. Our study confirms previous work regarding TTC as those who did choose FP received fertility information earlier in their diagnosis.

Among the 51% of patients who did not undergo FP, nearly 1/3 of these patients did desire FP, however, after initial fertility evaluation, were deemed inappropriate candidates for FP. Age and initiation of cancer treatment were the most significant contributors for poor fertility assessments. The authors believe fertility counseling with appropriate baseline fertility testing help patients make informed decisions about their future fertility and can immediately address reproductive concerns if patients are not FP candidates. Providing patients with information about their risks and options as well providing realistic expectations for future fertility will help alleviate some of the anger and distraught patients have with understanding their reproductive status long after their cancer treatment has ended.

This study has several strengths and limitations. This study included a population of all types of AYA cancer patients. The

American Society of Clinical Oncology recommends an Oncofertility referral for all AYA cancer patients³⁴ and so it is important to understand the needs of a diverse population of patients, not specific to gender or diagnosis. Additionally, this study collected information gathered at the time of diagnosis and decision making. Some of the factors that have contributed to the low utilization of FP in the past, such as knowledge and access to care, have been addressed in the study design. To limit any misclassification bias, all clinical data, such as diagnosis and treatment, were validated with electronic medical records. We excluded variables with greater than 10% missing data from the final analysis.

However, this was still a retrospective study and several limitations should be acknowledged. This study represents a population of AYA cancer patients who received a referral and completed an FP consult; thus, this approach may not be generalizable for all AYA cancer patients. One limitation related to the retrospective design is that we were unable to accurately predict temporality. This study looked at factors contributing to a clinical decision after a clinical fertility consultation. We were not able to measure if the patient decision was made before receiving an FP consult. Since the time a patient made their treatment decision cannot be accurately determined, findings from this study will be used to generate hypotheses for a phase-II study that will further investigate patient factors surrounding fertility expectations and treatment decision.

In recent years, new assisted reproductive technologies and emerging data for FP treatments have made FP a more widely available option for AYA patients facing a cancer diagnosis. Young adults have expressed sincere sadness and loss of hope in losing their fertility. It has also been suggested that informed decisions, following education and consultation, have assisted patients with understanding the risks of their cancer treatments, including infertility. It is important that all AYA cancer patients receive an opportunity to consider FP regardless of gender, age, relationship status, parity, insurance, diagnosis, or cancer treatment. Providing patients with an informed fertility consultation will lead to increased utilization of FP treatment by AYA cancer patients. Our findings support similar studies in which among patients receiving FP information, approximately 50% will go on to FP treatment.^{19,35} Furthermore, perceptions about patients' demographics or treatment characteristics do not predict FP utilization by AYA cancer patients.

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Author Disclosure Statement

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