Bendola Publishing
Journal of Fertility Preservation
Vol. 2 (2021), Article ID 246133, 4 pages
doi:10.32371/jfp/246133

Research Article

Access to Infertility Care and Utilization of a Regional Fertility Preservation Program for Cancer Patients

Jennifer Chae-Kim,[1] Robert Roman,[2] Tongil Kim,[3] and Larisa Gavrilova-Jordan[2]

[1]*Department of Obstetrics and Gynecology, College of Medicine, Texas A&M University, at Baylor Scott & White Health, Temple, TX 76508, USA*
[2]*Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Medical College of Georgia at Augusta University, Augusta, GA 30901, USA*
[3]*Department of Marketing, Naveen Jindal School of Management, University of Texas at Dallas, Richardson, TX 75080, USA*
Address correspondence to Jennifer Chae-Kim, jennifer.chaekim@bswhealth.org

Received 1 July 2021; Revised 9 August 2021; Accepted 12 August 2021

Abstract *Background.* Fertility preservation (FP) prior to gonadotoxic cancer treatment is underutilized in the United States (US) due to limited access to care. *Objective.* We aimed to determine the utilization of a regional FP program in an underserved region in the Southeast US. *Methods.* We performed an institutional review board-approved retrospective cohort study of patients enrolled in the FP program at an academic tertiary medical center from 2014 to 2018. *Results.* Sixty-nine reproductive age patients were enrolled in the FP program, including 29 men and 40 women between 20 and 49 years of age. Cancer diagnoses among the enrolled patients included hematologic ($n = 34$), breast ($n = 14$), testicular ($n = 11$), reproductive tract ($n = 7$), and gastrointestinal ($n = 3$) malignancies. Patients with reproductive tract malignancies were found to have approximately 9.7 times greater odds of proceeding with FP than patients with hematologic malignancies ($P < .05$). *Conclusion.* Utilization of a regional FP program should be considered to increase access to care to this critical resource for patients desiring future family building. Patients with hematologic malignancy may face unique barriers to FP.

Keywords fertility preservation; regional oncofertility; hematologic malignancy; reproductive tract malignancy; utilization

1. Introduction

Approximately 5,000 adolescents aged 15 to 19 and 60,000 adults aged 20 to 39 are diagnosed with cancer every year in the United States (US) [1]. Fortunately, overall survival rates are improving, and the vast majority survive cancer. In 2008–2014, 84.6% of adolescent cancer patients achieved 5-year remission [1,2]. Cancer treatments, however, may be gonadotoxic and impair fertility. Female cancer survivors, for instance, have an approximately 38% lower chance of pregnancy compared with the general population [3]. The gonadotoxic effect of cancer treatment depends on patient age, type of chemotherapy, radiation, or surgery, and duration of treatment. Alkylating agents such as cyclophosphamide and alkylating-like agents such as cisplatin or carboplatin are highly detrimental to primordial and pre-antral/antral follicles, granulosa cells, and spermatogonia [4]. Gonadotoxicity is increased when chemotherapy is combined with abdominal, pelvic, or testicular radiation [5]. Treatment may even necessitate the removal of one or both ovaries or testes.

There are established methods of fertility preservation (FP) for male and female cancer patients before cancer treatment. For female patients, FP options include embryo or oocyte cryopreservation, ovarian transposition, fertility-sparing surgery, and ovarian tissue cryopreservation. Embryo cryopreservation is the most well-studied FP method for women. Standard protocols for ovarian stimulation require two to six weeks. "Random start" protocols can be initiated at any time during the menstrual cycle and have been shown to decrease the time to starting cancer treatment and are as effective in oocyte retrieval as conventional protocols [6]. Oocyte cryopreservation is suitable for female patients without a male partner or sperm donor. However, oocyte and embryo cryopreservation does not protect ovaries against radiation damage, so the patient may still be at risk of post-treatment ovarian insufficiency. Other methods such as ovarian chemoprotection utilizing GnRH agonists during chemotherapy may be helpful if cryopreservation is not feasible or as an adjunct to reduce the probability of chemotherapy-induced ovarian insufficiency; however the efficacy of GnRH agonist therapy is not yet proven [7]. Ovarian tissue cryopreservation (OTC) is the only FP option available to prepubertal children and is no longer considered experimental [8]. Ovarian tissue transposition carries the risk of transplanting malignant cells after re-grafting. Ovarian transposition or oophoropexy can be utilized in patients undergoing abdominal or pelvic radiation. For male patients, FP options include semen cryopreservation and gonadal shielding from radiation [5].

Physician counseling of potential fertility outcomes is critical. Unfortunately, the gonadotoxic effects of cancer

therapy may be under-appreciated. One study showed that only 9% of patients received information about the fertility risk of cancer treatments or FP options, at a cancer center in the US [9]. Guidelines set by several organizations, including the American Society of Clinical Oncology (ASCO) and the American Academy of Pediatrics (AAP), encourage FP counseling and early referral to reproductive endocrinology [7]. Lack of FP counseling can be a source of significant distress for cancer survivors. Regarding the risk or reality of infertility, patients have reported feelings of depression, anxiety, and intense psychological distress [10,11]. In a study of female cancer survivors who were not counseled about potential infertility risk, those who later experienced infertility reported feelings consistent with post-traumatic stress disorder [11]. Surveys of adolescents have shown that they value parenthood in the future, even if it is not a short-term goal for them [12,13]. Even for those patients who did not pursue FP after counseling, they report better quality of life and less distress about infertility risk [14].

This study's FP or "oncofertility" program was established to meet these needs of cancer patients in an underserved region in the Southeast US. While FP can profoundly impact patients' lives, little is known about which patients pursue FP or which FP methods are preferred over other management, particularly among patients with limited access to care. In this study, we aim to answer these questions by assessing the utilization of a regional FP program within a multidisciplinary health care system.

2. Materials and methods

This was an institutional board review-approved retrospective cohort study at a university tertiary care facility in the state of Georgia, US. Waiver of informed consent was obtained. A retrospective chart review was performed of patients enrolled in the FP program between September 2014 and May 2018. The FP program of this study, which was established in September 2014, is the first formal oncofertility program in the area. Patients were counseled about the risk of cancer treatment on fertility and available FP options. If they elected for FP, they underwent a treatment method that was tailored to their clinical scenario. Chart review was performed to identify characteristics of the study population. The primary outcome assessed was whether patients pursued FP. Secondary outcomes were to examine whether the decision for FP correlated with characteristics such as demographics, malignancy type, whether the patients were seen on an inpatient versus outpatient status, or specific FP methods. Live birth outcomes were also examined. Statistical analysis of whether patients pursued FP was performed using logistical regression models in STATA with a P-value $< .05$ to determine statistical significance. De-identified data can be provided upon request.

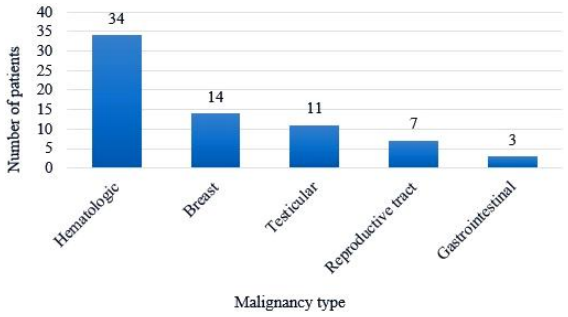

Figure 1: The figure shows the types of malignancy diagnoses among the study patients. Almost half of the enrolled patients had been diagnosed with hematologic cancer. The second most common malignancy was breast cancer.

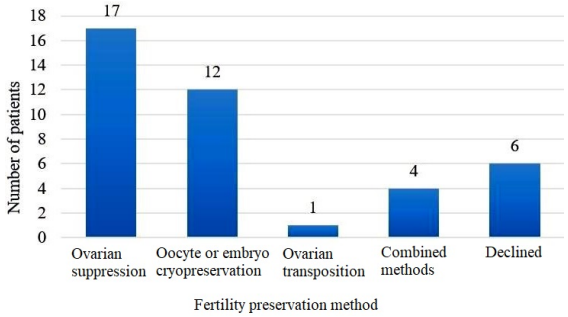

Figure 2: The figure demonstrates FP methods utilized by female patients. Combined methods to optimize ovarian preservation include medical ovarian suppression during chemotherapy or ovarian transposition before radiation.

3. Results

A total of 69 patients, including 40 females and 29 males, utilized the FP program. The average age of females was 28.8 ± 5.9 years and males 28.6 ± 6.4 years. About three-fourths of patients were seen on an outpatient basis. Majority of cancer diagnoses were hematologic ($n = 34$), followed by breast ($n = 14$), testicular ($n = 11$), reproductive tract ($n = 7$), and gastrointestinal ($n = 3$) (Figure 1).

Female patients underwent medical ovarian suppression ($n = 17$), embryo or oocyte cryopreservation ($n = 12$), ovarian transposition ($n = 1$), or combined methods ($n = 4$), and six patients declined to proceed with treatment. Of note, OTC was not offered to subjects as it was an experimental method of FP at the time of the study. Fifteen male patients underwent successful semen cryopreservation, while three patients had unsuccessful attempts (two patients had azoospermia, and one patient was unable to collect a specimen), and 11 declined treatment (Figures 2 and 3). An informal survey of reasons for declining FP included health status, financial burden or time limitations. In total, 34 female and 15 male patients pursued FP, and four live births resulted.

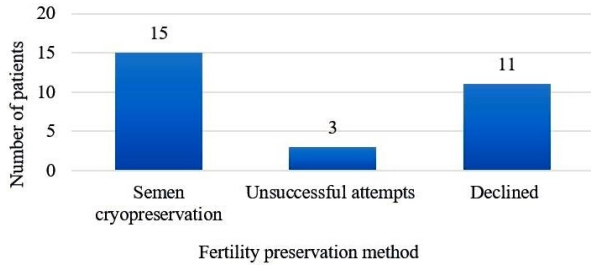

Figure 3: The figure demonstrates FP methods utilized by male patients.

Table 1: Statistical analysis using logistical regression models in STATA. Statistically significant P-value $< .05$. The baseline diagnosis is hematologic malignancies, which was the most common subset of diagnoses in the study population.

Variable	Odds ratio	Std. err.	P-value
Age	1.049	0.066	.448
Male	1.147	0.953	.869
Inpatient status	2.779	2.503	.257
Diagnosis (unknown)	0.398	0.431	.395
Diagnosis (other solid tumors)	2.678	2.53	.297
Diagnosis (reproductive tract malignancy)	9.689	10.637	.039
Constant	0.189	0.375	.401

Statistical analysis using logistical regression models showed that patients with reproductive tract malignancies had 9.7 times greater odds of proceeding with FP than patients with hematologic malignancies ($P < .05$). Other demographic variables and diagnoses did not significantly predict whether patients pursued FP (Table 1).

4. Discussion

Our study investigated which patients pursued FP, as this was not well known in our study population or the literature. Although all patients included in the study were counseled on FP, we found that patients with reproductive tract malignancies were more likely to proceed with FP methods than patients with hematologic malignancies. This result is consistent with previous studies that have found that the likelihood of receiving FP counseling was associated with a cancer diagnosis and that the proportion of patients with gynecologic cancers who were counseled was significantly higher than those with nongynecologic cancer [10].

Despite patients with hematologic malignancies comprising nearly half of our study population, they had significantly lower odds of proceeding with FP, suggesting there are barriers specific to this patient population. Patients with acute leukemia or lymphoma may require emergent therapy and may be unable to delay treatment for even a week needed to perform emergent in vitro fertilization [15]. In the context of an accelerated timeline to treatment, these patients may not receive FP counseling or referrals to reproductive endocrinology. Furthermore, these patients may be too clinically unstable to undergo standard FP options at the time of diagnosis. Patients with hematologic malignancies may have myelosuppression and may be more predisposed to bleeding complications from oocyte retrieval, limiting opportunities for FP in some cases. Treatment of non-Hodgkin's lymphoma often requires gonadotoxic doses of cyclophosphamide [15]. These considerations all pose significant barriers to treatment, and the results of our study affirm that patients with hematologic malignancies face unique barriers to care. Patients in this study were not offered OTC due to its experimental nature at the time of the study; future research should examine outcomes for patients with hematologic malignancies who undergo OTC given the unique time and health limitations faced, and given that many FP options may not be available to these patients. As there are more than a million survivors of Hodgkin and non-Hodgkin's lymphoma in the US every year, and nearly a fifth are patients of reproductive age [15], this is a crucial population of patients that should be targeted for FP services to close the gap in access to FP care.

Limitations of this research include the retrospective nature of the study. There are inherent biases in the referral and counseling process that may confound the results. Research suggests that males receive more counseling [16, 17] and referrals [18], and that women who already have children are less likely to receive referrals [9]. Although the patients in our study received referrals and counseling, we could not examine the referral rates for all patients diagnosed with cancer at our institution. This is an area of further research. It would be worthwhile to investigate whether higher referral rates for patients with certain cancer diagnoses may increase FP utilization. Access to FP may improve if referrals to reproductive endocrinology are routinely part of the cancer treatment process, with an established referral infrastructure in place [19]. Future directions in this research also include collecting data on the long-term outcomes in patients who received FP counseling and pursued an FP option. Another limitation of this study is the lack of data on specific reasons behind why patients proceed with FP. This could be a future avenue of research and provide direction for what aspects of FP counseling patients find most useful.

It should be noted that cost was a commonly cited reason why patients did not pursue FP. The study did take place in a state in which infertility care is not mandated. Further advocacy is necessary to overcome financial barriers to FP. Even if patients are adequately counseled and referred to RE on time, the cost of FP may be prohibitive. Most insurance companies, including Medicaid, do not cover the expenses of FP for cancer patients except in a few mandated states; thus, coverage remains elusive [20]. These barriers amount

to cancer patients' inability to protect their reproductive health, facing the risk of infertility after cancer treatment.

5. Conclusion

In conclusion, this study examines the utilization of FP services in an underserved region in the Southeastern US, and identifies patients with reproductive tract malignancies as a patient population likely to proceed with FP, relative to patients with hematologic malignancies. The study results demonstrate increased access to care in this underserved region, which did not have formal oncofertility services prior to initiation of the FP program. The utilization of the regional FP program should be considered to increase access to care to this critical resource for patients desiring future family building.

Funding This research was not supported by any funding.

Acknowledgments The authors would like to thank the Augusta University Oncofertility Program. This manuscript is based on an abstract presented at the 2019 annual conference of the South Atlantic Association of Obstetrics and Gynecology.

Conflict of interest The authors declare that they have no conflict of interest.

References

[1] A. M. Noone, N. Howlader, M. Krapcho, D. Miller, A. Brest, M. Yu, et al., eds., *SEER Cancer Statistics Review, 1975–2015*, National Cancer Institute, Bethesda, MD, 2019. https://seer.cancer.gov/csr/1975_2015/.

[2] R. L. Siegel, K. D. Miller, and A. Jemal, *Cancer statistics, 2018*, CA Cancer J Clin, 68 (2018), 7–30.

[3] European Society of Human Reproduction and Embryology, *Female cancer survivors are one-third less likely to achieve pregnancy than women in general population*, https://www.sciencedaily.com/releases/2017/07/170703101404.htm, 2017.

[4] A. Yuksel, G. Bildik, F. Senbabaoglu, N. Akin, M. Arvas, F. Unal, et al., *The magnitude of gonadotoxicity of chemotherapy drugs on ovarian follicles and granulosa cells varies depending upon the category of the drugs and the type of granulosa cells*, Hum Reprod, 30 (2015), 2926–2935.

[5] J. L. Moss, A. W. Choi, M. K. Fitzgerald, Keeter, and R. E. Brannigan, *Male adolescent fertility preservation*, Fertil Steril, 105 (2016), 267–273.

[6] G. Bedoschi and K. Oktay, *Current approach to fertility preservation by embryo cryopreservation*, Fertil Steril, 99 (2013), 1496–1502.

[7] K. Oktay, B. E. Harvey, and A. W. Loren, *Fertility preservation in patients with cancer: ASCO clinical practice guideline update summary*, J Oncol Pract, 14 (2018), 381–385.

[8] M. B. Moravek, L. C. Appiah, A. Anazodo, K. C. Burns, V. Gomez-Lobo, H. R. Hoefgen, et al., *Development of a pediatric fertility preservation program: A report from the pediatric initiative network of the oncofertility consortium*, J Adolesc Health, 64 (2019), 563–573.

[9] S. B. Goldfarb, S. A. Kamer, B. A. Oppong, A. Eaton, S. Patil, M. J. Junqueira, et al., *Fertility preservation for the young breast cancer patient*, Ann Surg Oncol, 23 (2016), 1530–1536.

[10] A. Ameri, K. Novin, A. Sourati, and P. Rashidi, *Awareness of female cancer patients about the risk of impaired fertility*, J Adolesc Young Adult Oncol, 8 (2019), 342–348.

[11] T. K. Woodruff, *Fertility lost-fertility found: narratives from the leading edge of oncofertility*, Narrat Inq Bioeth, 7 (2017), 147–150.

[12] J. F. Taylor and M. A. Ott, *Fertility preservation after a cancer diagnosis: A systematic review of adolescents', parents', and providers' perspectives, experiences, and preferences*, J Pediatr Adolesc Gynecol, 29 (2016), 585–598.

[13] D. Hoeg, L. Schmidt, and K. T. Macklon, *Young female cancer patients' experiences with fertility counselling and fertility preservation—a qualitative small-scale study within the Danish health care setting*, Ups J Med Sci, 121 (2016), 283–288.

[14] L. Bastings, Ö. Baysal, C. C. Beerendonk, J. IntHout, M. A. Traas, C. M. Verhaak, et al., *Deciding about fertility preservation after specialist counselling*, Hum Reprod, 29 (2014), 1721–1729.

[15] A. W. Loren, *Fertility issues in patients with hematologic malignancies*, Hematology Am Soc Hematol Educ Program, 2015 (2015), 138–145.

[16] G. M. Armuand, K. A. Rodriguez-Wallberg, L. Wettergren, J. Ahlgren, G. Enblad, M. Höglund, et al., *Sex differences in fertility-related information received by young adult cancer survivors*, J Clin Oncol, 30 (2012), 2147–2153.

[17] R. S. Barbour, M. A. Porter, V. L. Peddie, and S. Bhattacharya, *Counselling in the context of fertility and cancer: some sociological insights*, Hum Fertil (Camb), 16 (2013), 54–58.

[18] M. A. Arafa and D. M. Rabah, *Attitudes and practices of oncologists toward fertility preservation*, J Pediatr Hematol Oncol, 33 (2011), 203–207.

[19] A. Anazodo, P. Laws, S. Logan, C. Saunders, J. Travaglia, B. Gerstl, et al., *How can we improve oncofertility care for patients? a systematic scoping review of current international practice and models of care*, Hum Reprod Update, 25 (2019), 159–179.

[20] G. N. Algarroba, J. S. Sanfilippo, and H. Valli-Pulaski, *Female fertility preservation in the pediatric and adolescent cancer patient population*, Best Pract Res Clin Obstet Gynaecol, 48 (2018), 147–157.