

**RESEARCH ARTICLE****Implementation of an Oncofertility Program: Key Elements, Challenges, and Solutions of the Oncofertility Treadmill****Authors**

Anisa Hussain MA<sup>1</sup>, Jacqueline Sehring MA<sup>1</sup>, Safina Usmani MA<sup>1</sup>, Lauren Grimm MA<sup>1</sup>, Ahmad Abadi MD<sup>2</sup>, Angeline Beltsos MD<sup>1</sup>, Roohi Jeelani MD<sup>1</sup>

**Affiliations**

<sup>1</sup>Vios Fertility Institute, 1455 N Milwaukee Ave, Chicago, IL 60622, United States

<sup>2</sup>Wayne State University Department of Obstetrics & Gynecology, 3990 John R. Street, 7 Brush North, Detroit, MI, 49201, United States

**Corresponding author:**

Anisa Hussain

EMAIL: [afh.930@gmail.com](mailto:afh.930@gmail.com)

(630) 373-9416

1455 N Milwaukee Ave, Chicago, IL 60622

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**Abstract**

An overwhelming proportion of females of reproductive age are affected by cancer annually. As the efficacy of cancer treatments increases the number of cancer survivors, it is imperative to ensure that the fertility-related needs of cancer survivors are met. Given the gonadotoxic nature of many cancer treatments, fertility preservation for patients prior to cancer treatment, Oncofertility, is a critical area of reproductive care. The establishment of an Oncofertility program requires swift and effective patient care that relies heavily on collaboration between multiple specialties, patient education, and clear treatment protocol. This specific flow of patient care can be referred to as an “Oncofertility treadmill,” given the emphasis on efficiently completing ovarian hyperstimulation cycles so that the patient may proceed with cancer treatment. We began by identifying key steps in the establishment of an Oncofertility program at a private, multisite fertility clinic, then explored the challenges that providers and patients may face, and the outcomes of Oncofertility patients undergoing ovarian hyperstimulation with the intention of oocyte cryopreservation. Oncofertility care is complex and the establishment of concrete guidelines for this Oncofertility care will greatly benefit cancer survivors.

**Keywords:** clinical guidelines, fertility preservation, oncofertility, fertility treadmill

## 1. Introduction

### 1.1 Cancer Survival and Fertility Preservation

The World Health Organization (WHO) estimated that 1.8 million people would be diagnosed with cancer in 2020.<sup>1</sup> More than 50% of these patients would be female, and a large proportion of these female patients would be of reproductive age.<sup>1</sup> Therefore, care surrounding this unique patient population is critical. Of note, an estimated 85% of women under age 45 with a cancer diagnosis survived from 2008-2014.<sup>2</sup> Many of these positive clinical outcomes can undoubtedly be attributed to the vast improvements in cancer prevention, screening, detection, and treatment.

Although advancements in these areas of research lead to more cancer survivors, the need for care does not end with the end of the patient's successful cancer treatment. Many effective cancer treatments have gonadotoxic potential, which can have tremendous impact on survival quality of life. Specifically, many female cancer survivors of reproductive age experience acute ovarian failure.<sup>3,4</sup> The impact of infertility on quality of life is well-documented, with most studies concluding that infertile patients, especially females, have diminished quality of life associated with infertility. In fact, a qualitative study in 2019 exploring the conflicts faced by breast cancer patients concluded that fears related to future child-bearing was the primary dilemma for patients considering different treatment methods and plans.<sup>5</sup> The goal of oncofertility, or fertility preservation prior to cancer treatment, is to address this dilemma.

Fertility preservation is offered to cancer patients prior to beginning cancer treatment in order to protect their quality of life after cancer, safeguarding their fertility, so that the option for family planning exists for them after successful cancer treatment.

### 1.2 Oncofertility Treadmill

Oncofertility relies heavily on quick action. Soon after the cancer diagnosis, patients are referred for fertility preservation, treated, and exited as efficiently as possible. Following fertility treatments, patients are able to promptly begin their cancer treatment as planned. "Fertility treadmill" refers to the quick, machine-like cycling of oncofertility patients in and out of the clinic. Rapid evaluation by reproductive endocrinologist (RE), clear communication with the oncology team, and efficient care from the fertility practice support staff ensures that the fertility treadmill remains intact. Treatment timeline, financial constraints, and risks associated with treatment must all be taken into account when counseling each individual oncofertility patient. While several studies exist exploring the shortcomings of oncofertility treatment in general, few guidelines exist for the real-world application of oncofertility practice.

Addressing fertility within the context of a cancer diagnosis creates a sense of urgency to complete fertility preservation as quickly as possible so that the patient may proceed with the necessary treatment for their cancer. While the preservation of the patient's life is of the most immediate importance, preservation of fertility cannot be overlooked. Therefore, it is necessary to create practice guidelines under which fertility preservation treatments can be completed quickly and effectively, without interfering with or delaying cancer treatment. The aim of this study is to outline the stepwise process of implementing an oncofertility program in practice at a private fertility clinic. The following is a report on the implementation of the oncofertility treadmill system in a private, multisite fertility clinic, as well as a discussion of patient care and outcomes within such a system.

## 2. Method

Retrospective chart review was conducted

at a multisite fertility clinic located in the midwestern United States. Patients undergoing controlled ovarian hyperstimulation from 2017 through 2020 with the intention of oocyte retrieval were included. Inclusion criteria were defined as female patients undergoing hormonal stimulation with the intention of oocyte retrieval in response to a new (active) cancer diagnosis, and prior to beginning cancer treatment. Patients who met this criteria were included in the experimental group. Exclusion criteria were previous cancer treatment or lack of new(active) cancer diagnosis. This experimental group was identified as the “oncofertility” group and will be referred to as such. The control group consisted of patients undergoing hormonal stimulation for oocyte retrieval with no known cancer. Both the oncofertility and control groups were then further subdivided into groups based on age (< 35 years and 35+ years), resulting in a total of four groups, 2 oncofertility and 2 control.

All patients underwent the antagonist IVF protocol. The patients were treated with self-administered follicle stimulating hormone (FSH) and a GnRH antagonist until the day of the oocyte maturation trigger injection. Of note, due to the fast pace of the oncofertility treadmill, patients began administering medications as early as possible, rather than waiting for the beginning of the follicular phase of the menstrual cycle, as is common with non-oncofertility ovarian hyperstimulation treatment.

Treatment protocols were modified on an individual basis by RE to minimize risk for oncofertility patients (see Discussion). Patients for whom supraphysiologic estrogen was deemed a risk were administered letrozole, which prevents the biosynthesis of estrogen, alongside FSH. Patients at low risk for ovarian hyperstimulation syndrome (OHSS) received a human chorionic gonadotropin (hCG) trigger injection. Those patients noted to be at high risk for OHSS received a dual GnRH agonist-hCG trigger injection to prevent OHSS-associated

complications. Data was analyzed by unpaired t-test (GraphPad Software, LLC). The study received Western Institutional Review Board (IRB) exemption under 45 CFR 46.101(b)(4).

Following quantitative data collection each patient chart was reviewed individually to gather data on patient history, referral to the clinic, correspondence between oncology and fertility specialist teams, and communication. This information was then compiled to create a guide in overcoming common challenges in oncofertility care (see Discussion).

### 3. Results

Of the 18 oncofertility patients identified in the study, all 18 were referred for reproductive counseling by the physician providing cancer-related care. 2 patients did not pursue fertility preservation beyond the initial consultation with a RE. The first patient cancelled treatment due to financial constraints. The second patient no longer pursued treatment based on joint recommendation from RE and the oncologist providing care, who advised that the risk of spreading ovarian cancer during oocyte retrieval was too high, given imaging. Of note, one endometrial cancer patient was approved to undergo two cycles of ovarian stimulation for oocyte cryopreservation.

Therefore, 17 total complete oncofertility cycles were identified. Cancer types included ovarian cancer, breast cancer, cervical cancer, endometrial cancer, rectal cancer, and Hodgkin’s lymphoma. Of note, 2 patients under 35 years and 4 patients 35 years and above underwent random start. 6 patients under 35 years and 2 patients 35 years and above required the addition of letrozole. The remaining patients underwent conventional start.

There was no significant difference in the average AMH nor in the amount of follicle stimulating hormone (FSH) received by patients, when comparing oncofertility and control groups. The average AMH of oncofertility patients below 35 years of age

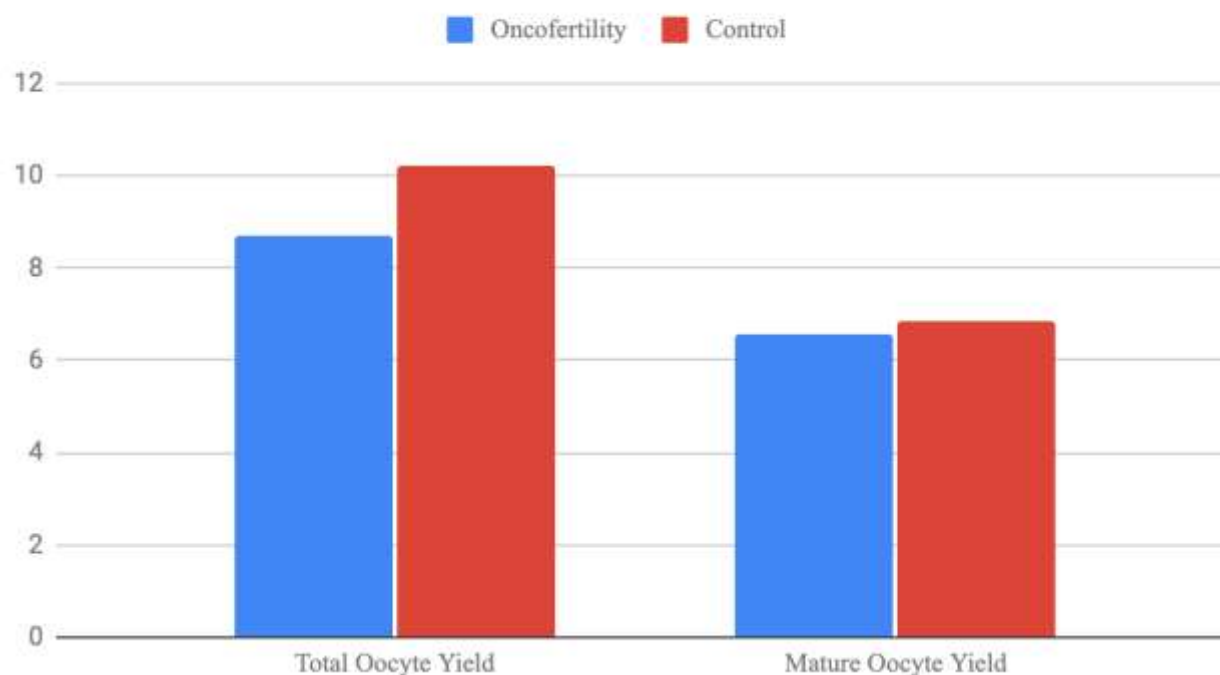
was 3.65 ng/ml, while the average AMH of control patients in the same age group was 1.93 ng/ml. The average AMH of oncofertility patients 35 years or older was .69 ng/ml, while the average AMH of control patients in the same age group was 1.64. The average FSH and length of stimulation for oncofertility patients under 35 years was 3,133 units over

the course of approximately 11 days, while control patients in the same age group received 4,288 units over the same time period. The average FSH and length of stimulation for oncofertility patients 35 years and older was 4,575 units over 11 days, while control patients of the same age demographic received 5,423 units over 13 days (Table 1).

**Table 1:** Average FSH (units), AMH (ng/mL), and length of treatment for oncofertility and control patients, subdivided by age into two groups: below 35, and 35 and above

	Oncofertility		Control	
	Below 35	35 and Above	Below 35	35 and Above
FSH (units)	3133.33	4575	4288.33	5423.33
AMH (ng/mL)	3.65	0.69	1.93	1.64
Treatment length (days)	10.88	11.54	10.6	13.07

### Total and Mature Oocyte Yield in Patients 35 Years and Above

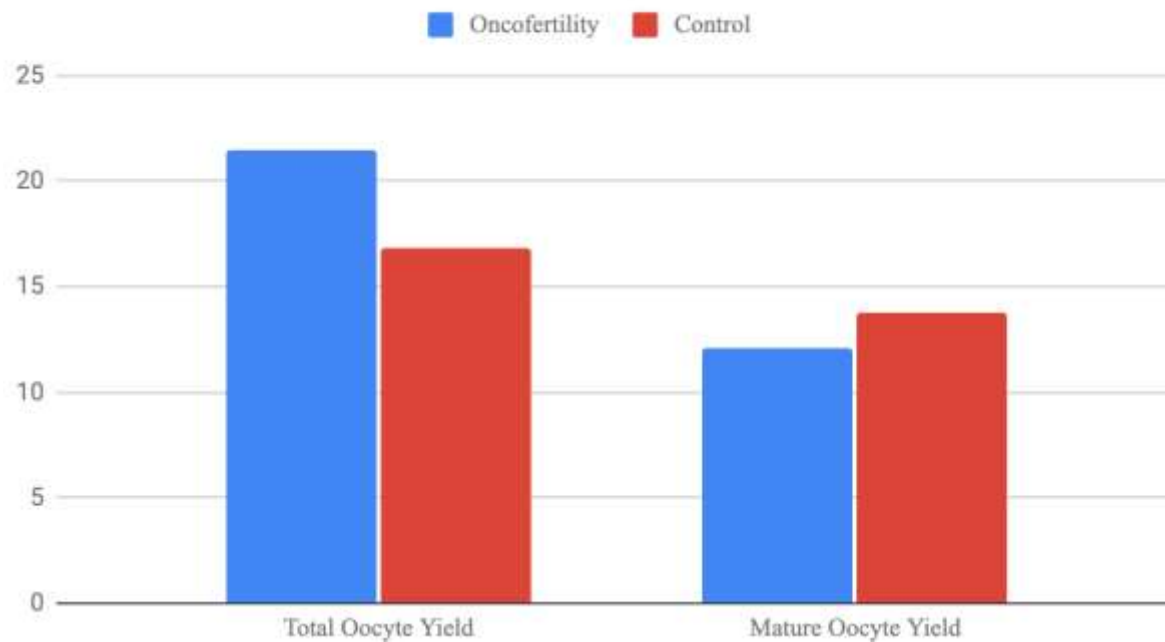


**Figure 1:** Oncofertility patients 35 years and above had a total average oocyte yield of 8.71, while control patients of the same age cohort had a total average oocyte yield of 5.57. Mature oocyte yield was 6.57 and 6.87 for oncofertility and control patients of this age group, respectively. No significant difference noted ( $p=.67$  and  $p=.89$ ).

In patients aged 35 years or above, there was no significant difference between the total number of oocytes retrieved ( $p=.67$ ), nor in the proportion of oocytes retrieved that were mature ( $p=.89$ ) in oncofertility and healthy patients. In oncofertility patients in this age group, an average of 8.71 oocytes were retrieved, while an average of 6.57 were mature. In healthy patients in this age group, an average of 10.2 oocytes were retrieved and an average of 6.87 were mature. Oncofertility patients 35 years and above matched healthy controls in both total oocytes retrieved and, more importantly, mature oocyte yield (Figure 1).

However, in patients younger than 35 years, while there was no significant difference in the oocyte yield between oncofertility and healthy patients ( $p=.27$ ), oncofertility patients had a significantly smaller proportion of mature oocytes ( $p<.05$ ). On average, oncofertility patients in this age group had 21.44 oocytes retrieved, an average of 12.11 of which were mature. Healthy patients in the same age group had 16.8 oocytes retrieved with 13.73 mature. Again, although there was no significant difference in the total number of oocytes retrieved, a significantly smaller number of oncofertility oocytes were mature (Figure 2).

### Total and Mature Oocyte Yield in Patients 34 Years and Below



**Figure 2:** Oncofertility patients 34 years and below had an average oocyte yield of 21.44, while control patients of the same age group had an average oocyte yield of 16.8 ( $p=.27$ ). Within this age group, oncofertility patients had a mature oocyte yield of 12.11, while control patients had 13.73 ( $p<.05$ ).

## 4. Discussion

### 4.1 Identifying the key figures of the oncofertility treadmill

Fertility preservation may not be the patient's primary concern in response to a new

cancer diagnosis, however, future fertility has a significant impact on patients' decision-making. A survey conducted amongst breast cancer patients revealed that 73% of patients were concerned about the possibility of treatment-induced infertility. This concern impacted the care-related decisions made by

29% of respondents (Patridge 2004). At this point, an oncologist may refer the patient to an RE to explore fertility preservation options. However, the same survey reported that these concerns were adequately addressed only 51% of the time (Patridge 2004). The trend of unaddressed oncofertility concerns is further supported by a 2019 study that revealed that fewer than 15% of oncologists regularly refer patients to reproductive specialists.<sup>6</sup> Oncologists participating in the study cited reasons such as poor prognosis, cost of fertility preservation treatment, and lack of knowledge (Anazodo 2019). Interestingly, one study showed that 40% of clinicians thought that the topic of fertility preservation should be broached by the patient, rather than offered by the oncologist (Ghorbani 2011).<sup>7</sup>

These studies indicate that the first barrier to care is referral, followed by the oncologist's specific concerns regarding fertility preservation. Strong working relationships between oncologists and fertility specialists and a coordinated referral process are critical to overcoming this barrier.<sup>8</sup> In our study, the referral process was supplemented by a referral form to be completed by the oncologist upon the fertility specialist's acceptance of care. 100% of oncofertility patients were referred by their oncologist. The establishment of an oncofertility patient population at a fertility clinic, is therefore, critically dependent on an oncologist. The oncofertility patient's "start" takes place with the oncologist. The oncologist, therefore, plays a critical role in the oncofertility treadmill.

Direct communication between RE and oncologist regarding fertility preservation took place in 100% of cases. Following initial fertility preservation consultation with the patient, oncologist approval was required for pursuit of treatment. As such, decisions to pursue or cancel treatment were made based on joint recommendations and approval from oncologist and RE. For example, one patient's cancer treatment timeline allowed for two oocyte cryopreservation cycles to be

completed prior to treatment. Contrastingly, one patient's cancer proved incompatible with oocyte retrieval; the cycle was canceled because the risk of spreading cancer to the peritoneum and vagina was deemed too great by the oncologist. Such cases reiterate that the oncofertility treatment is not independent from the cancer diagnosis.

## 4.2 Drug Protocol

Drug protocols in healthy patients vary vastly based on age, endocrine profile, genetic background, fertility history, and many other factors. When treating an oncofertility patient, these determinants of treatment must be balanced with limitations specific to the cancer. Random vs. conventional start, the addition of letrozole, and the trigger prescribed for ovulation induction were all determined with the cancer diagnosis taken into account.

A reason commonly cited for hesitancy among oncologists to refer patients for oncofertility care prior to treatment is the fear of delaying cancer treatment (Anozado 2019). Conventional ovarian hyperstimulation begins early in the follicular phase of the menstrual cycle. However, waiting to begin treatment at a specific point in the patient's menstrual cycle may result in significant delays in cancer therapy initiation. Of note, approximately 60% of oncofertility patients included in the oncofertility program underwent random-start treatment.

"Random-start" refers to treatment beginning at any point of the menstrual cycle, as opposed to conventional start, in which ovarian stimulation occurs throughout the follicular phase of the menstrual cycle. It has been generally understood that antral ovarian follicular development takes place exclusively during the follicular phase. Therefore, conventional ovarian stimulation protocols begin stimulation during the follicular phase and continue monitoring the ovaries through the follicular phase before inducing ovulation. However, recent studies show that 50% of healthy women have antral ovarian follicular

development during the luteal phase.<sup>9</sup> This discovery is the basis of random start protocols, in which stimulation begins at any time during the menstrual cycle. Studies suggest that random start is an effective treatment protocol in patients with cancer.<sup>10</sup> The theme prevailing throughout oncofertility treatment is urgency, therefore treatment timeline is of the utmost importance in these treatment cycles. The addition of random start to oncofertility protocols addresses this fear.

The supraphysiological levels of estrogen achieved in ovarian hyperstimulation poses a unique risk to those patients whose cancer may respond to estrogen. In such cases, the addition of selective estrogen receptor modulators (SERMs) or aromatase inhibitors should be considered. For this reason, a total of 7 of 16 oncofertility cycle protocols included letrozole, an aromatase inhibitor.

The final step in the ovarian hyperstimulation process, the trigger, is largely determined by the risk of ovarian hyperstimulation syndrome (OHSS).<sup>11</sup> OHSS primarily presents with minor symptoms such as abdominal fullness, nausea, and vomiting. However, more severe presentations include electrolyte imbalance and fluid overload, resulting in ascites or pulmonary edema that may lead to hospitalization. The complications associated with OHSS may be amplified in the context of oncofertility. One study showed that hospitalized, non-pregnant patients with OHSS required approximately 8 days from the day of hospitalization for complete recovery.<sup>12</sup> Most oncofertility patients only have enough time to allow for one cycle of ovarian stimulation, so REs may be tempted to pursue aggressive stimulation. However, the potential for OHSS and the subsequent delay of cancer treatment initiation disallow aggressive treatment.

Additionally, studies show that patients administered a GNRH agonist trigger, have significantly lower incidence of OHSS, compared to patients administered an hCG trigger.<sup>13</sup> Several studies suggest that a dual trigger (GNRH agonist with low dose hCG) also minimize the risk of OHSS while

maximizing oocyte yield.<sup>14</sup> Therefore, in order to optimize oocyte maturation while minimizing the risk of OHSS and its potential complications, 100% of patients received a dual trigger. Of note, 1 patient was diagnosed with mild OHSS following oocyte retrieval. However, the case was mild and the patient was not hospitalized, so OHSS did not lead to a significant delay in treatment.

An effective oncofertility treadmill requires that the cancer diagnosis and impending treatment be taken into account at every step of patient care. Determining treatment start, the drugs involved in ovarian stimulation, and the ovulation induction method all require optimizing patient outcomes while minimizing risks.

### 4.3 Patient outcome

As the goal of the oncofertility treadmill is fertility preservation, patient outcomes cannot be ignored when implementing this program. Although cancer does not discriminate with age, it is no secret that the fertility and infertility experience does change drastically with female age. According to the American College of Obstetricians and Gynecologists, a gradual yet significant age-related decline in female fertility begins at 32 years before a more drastic decline beginning around 37 years.<sup>15</sup>

Our results indicate that a cancer diagnosis does not change ovarian response in patients 35 years or older, therefore, patients in this category undergoing fertility preservation prior to gonadotoxic treatment may be counseled based on age and AMH and ovarian stimulation may begin beyond the follicular phase of their menstrual cycle. The lack of statistical difference between oncofertility and healthy patients 35 years and above may be accounted for by the fact that ovarian response to hormonal stimulation diminishes with age. However, oncofertility patients younger than 35 years had a significantly lower proportion of mature oocytes, compared to controls. It is

widely accepted that the inflammatory state of cancer decreases ovarian response and oocyte quality.<sup>16, 17</sup> While it is possible that the inflammation associated with cancer accounts for the diminished ovarian response in oncofertility patients younger than 35, further studies must be conducted to fully understand the mechanism behind this phenomenon.

Exploring the incorporation of anti-inflammatory medications, such as antihistamines, into the IVF protocol of oncofertility patients in further studies in order to determine if battling the inflammation associated with cancer results in age and AMH-appropriate response to ovarian hyperstimulation is warranted.

## **5. Conclusion**

The need for oncofertility treadmill implementation is clear, with rising rates of cancer in females of reproductive age. Establishing an oncofertility program in a fertility practice requires a formal referral program and clear communication between oncology and fertility practitioners. Upon establishment of care for fertility preservation, patient treatment plans are

determined based on recommendations from oncology and fertility specialists. Throughout ovarian stimulations, oncofertility patients must be monitored for possible OHSS in order to optimize clinical outcomes while minimizing risks and potential delay of cancer treatment initiation.

When patients are counseled for fertility preservation under the guidance and approval of an oncology team, oncofertility patients over age 35 appear to respond to treatment in a similar way to healthy controls, while oncofertility patients under the age of 35 may not be as responsive to treatment as healthy controls. Further studies on fertilization rates, implantation rates, and live birth outcomes are necessary to fully understand the quality of oncofertility oocytes. This study supports the establishment of a formal oncofertility program at private fertility clinics in order to meet cancer patients at their unique point of need.

### **Ethical approval:**

The study received Western Institutional Review Board (IRB) exemption under 45 CFR 46.101(b)(4).



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