



Cancer and Fertility: State of the Art and Future Directions

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Abstract

Early menopause and infertility are common consequences of antineoplastic treatments in premenopausal women. Since the ability to have biological children is of great importance for cancer survivors, the risk of infertility is a source of great distress and lower quality of life among these patients. Several procedures can be presented to both men and women at the time of diagnosis. Despite increasing awareness, fertility in cancer is not universally discussed, in spite of the American Society of Clinical Oncology (ASCO) latest recommendations.

This review summarized and contextualized the existing research that has been conducted on oncofertility, while reflecting on future research and clinical directions, aiming to optimize patient care.

Keywords: cancer, oncology, survivors, fertility, oncofertility

Introduction

Despite its higher incidence in postmenopausal women, cancer is increasingly common in women of childbearing age (Assi et al., 2013). Besides breast cancer, cervical cancer, thyroid cancer, non-Hodgkin's lymphoma and leukemia are the most frequent cancers among men and women younger than 40, with little difference between different countries (Fidler et al., 2017).

Advances in early diagnosis and improved treatment protocols have significantly increased these patient survival rates, now exceeding 80% for some cancer types (Allemani et al., 2018). These higher survival rates increase the importance placed on survivorship issues, such as quality of life and the multitude of challenges after successful treatment (Anderson et al., 2018). Changes in fertility are a potential adverse effect of cancer and the neoplastic treatments.

With the recent voluntary deferral of procreation in Western societies, many of these men and women, at the time of diagnosis, have yet to initiate family or have not yet completed their family wishes. Although surrogacy and adoption can be an option, many cancer survivors voice a preference for biological parenting (Oktay & Oktem, 2009). Since thousands of cancer patients and survivors are in their reproductive age, the risk of infertility after cancer and its impact on quality of life, assumes great clinical significance.

In this context, *Oncofertility* appeared as an emerging discipline aiming to understand cancer patients needs regarding their reproductive potential before, during and after antineoplastic treatments (Woodruff, 2010). As a new clinical specialty, it also advocates for the timely provision of fertility information and for the referral to fertility preservation specialists to all cancer patients of reproductive age (< 45 years) (Logan, Perz, Ussher, & Anazodo, 2017), and for the importance of establishing fertility

preservation as a part of current medical practice in oncology (Loren et al., 2013; Oktay et al., 2018).

Methodology

To perform this review, a literature search was carried on the descriptors *cancer* and *fertility* in two different databases: PubMed and PsycInfo. No time restrictions were applied. Last search was performed in December 2018. This review included articles and other reviews addressing this topic.

Results

To optimize understanding, this review was subdivided into the following subheadings: effects of anticancer treatments on fertility; fertility preservation methods; international recommendations regarding infertility risk; health professionals' attitudes towards fertility preservation; patient's concerns and attitudes regarding risk of infertility; patients' information needs regarding fertility preservation; and the impact of the risk of infertility in patient's quality of life.

Effects of anticancer treatments on fertility

The negative effect of cancer therapy on fertility is well-known. Some chemotherapeutic agents, abdominal or pelvic radiation, bone marrow transplantation and surgery for gynecological malignancies, have a high risk of gonadal damage (Alvarez & Ramanathan, 2018). Especially chemotherapy and endocrine treatments, have experienced a significant increase in the last decade. These antineoplastic treatments may partially or definitively affect ovarian function and lead to early menopause with all of its inherent risks, including infertility, that may be temporary or permanent.

Adjuvant chemotherapy, particularly with alkylating agents (such as

cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, and procarbazine), poses the greatest risk of significant or permanent damages on fertility in both men and women (Oktay & Oktem, 2009). This agent is responsible for high gonadotoxicity and induces amenorrhea in 18 to 61% of women under 40 years. Women who receive this agent are four times more likely to develop ovarian failure, since it markedly accelerates the rate of age-related ovarian follicle loss by approximately 10 years (Kim, Klemp, & Fabian, 2011).

When fertility is preserved after chemotherapy, specifically in hormone-dependent breast cancer tumors, women are also prescribed with hormonal replacement therapy, such as tamoxifen. In these cases, women are advised to postpone their pregnancy for a minimum of two to five years, since the risk of recurrence is higher in this time period and this hormonal treatment is proposed for a minimum of five years. Nevertheless, extending tamoxifen up to ten years rather than stopping at 5, has been proven to further reduce recurrence and mortality, especially after the tenth year (Davies et al., 2013). This extension has been incorporated into the international guidelines for cancer treatment, preventing women from considering pregnancy, as fertility is also likely to be reduced due to age-related decline (Charif et al., 2015). Nevertheless, these patients should not be discouraged to become pregnant when they want to, since research suggested no adverse effect of pregnancy on survival (de Bree, Makrigiannakis, Askoxylakis, Melissas, & Tsiftsis, 2010). Furthermore, the research also revealed that local or systemic anticancer treatments posed no further risks for the offspring of cancer survivors. However, since there is a higher risk for miscarriage in these situations, there are some necessary prerequisites that should be considered when supporting a pregnancy after cancer. The interval between treatment and conception is one of the most important considerations, since

women who conceived less than one year after chemotherapy, had higher risks of preterm birth than women who conceived two years or more after treatment (Hartnett et al., 2018).

Fertility preservation methods

Increasing survival rates in oncology patients in reproductive age has led to the development and increasing use of various fertility preservation techniques. In male patients, because of advances in fertilization and sperm bank technologies, sperm cryopreservation is well-established, cheap and easily performed (Oktay & Oktem, 2009). In female patients, fertility preservation procedures are usually more expensive, time consuming, requiring of more medical expertise, and not as reliable as sperm banking in men. Nevertheless, given the importance of fertility, especially for female patients, there are different techniques that can be presented before treatment initiation, based on the patient's age and health status, as well as risk of ovarian involvement (Rajabi, Aliakbari, & Yazdekhashti, 2018)

Embryo cryopreservation is the most well-established option for female fertility preservation, as recognized by ASCO (American Society of Clinical Oncology) and ASRM (American Society for Reproductive Medicine) (Loren et al, 2013; Oktay et al., 2018). This procedure involves an ovary stimulation period with daily injections of gonadotrophins and ultrasonographic monitoring of follicle growth, which implies exposure to high levels of estrogen and a delay in systemic treatment commencement for at least two to three weeks. This method also implies that there is a source of male gametes, sometimes causing the exclusion of women who do not have a steady partner (Rajabi et al., 2018). In these situations, other viable options should be presented, including the cryopreservation of oocytes, which also require an ovarian stimulation procedure, a subsequent follicular puncture and

cryopreservation obtained by vitrification. This vitrification by freezing technique has significantly improved the survival of oocytes, fertilization rates and the ratio of high-quality embryos due to slow freezing, allowing better conservation results (Oktay et al., 2018).

In addition to these two methods, there are other experimental options, such as ovarian tissue cryopreservation, especially useful when hormonal stimulation is undesirable and/or there is urgency in anticancer treatment initiation. This technique, involves a laparoscopic surgery for harvesting a fragment of the ovary. Hereafter, the ovarian tissue is properly prepared and cortex fragments are isolated for cryopreservation. Whenever necessary, the fragments are thawed and grafted on the remaining ovary - orthotopic transplantation - or in another location - heterotopic transplantation. After transplantation, the ovarian tissue can restore its endocrine function and fertility (Rajabi et al., 2018). Concerning gonadotropin-releasing hormone agonist (GnRHa), evidence is still inconclusive regarding its isolated success for fertility preservation during chemotherapy (Oktay et al., 2018).

The American Society of Clinical Oncology (ASCO) has recently updated its guidelines for fertility preservation in cancer patients. If clinically safe and if the patient has time before treatment commencement, ASCO recommended that oocyte cryopreservation should be offered (Abdallah et al., 2017; Oktay et al., 2018). In addition, ovarian cryopreservation is another procedure with great potential in the near future (Rajabi et al., 2018).

Therefore, with the recent advances in biomedicine and technology, the probability of childbearing after aggressive antineoplastic treatments is constantly increasing. Nevertheless, fertility outcomes in oncology patients have not been adequately studied given the small percentage of patients that attempted to get pregnant after cancer. Many studies have

reported good results of these procedures, but only a few of them reported pregnancy outcomes in patients returning to use their embryos or oocytes after cancer (Alvarez & Ramanathan, 2018; Anderson et al., 2018).

International recommendations regarding infertility risk

ASCO recommendations regarding fertility preservation encouraged oncologists to address the risk of infertility with their patients treated during childbearing years, to discuss with them fertility preservation options and to refer them to reproductive specialists (Loren et al, 2013; Oktay et al., 2018; Oktay & Oktem, 2009).

First, patients should be informed about the feasibility of pursuing fertility preservation options and its dependency on each patient's recurrence risk, prognosis and risk of infertility or early menopause from oncology therapy. Next, fertility preservation options should be discussed with their respective success rates, including those considered experimental. Clinicians should also explain that these procedures may be time consuming and, therefore, subjected to time constraints and antineoplastic treatment delay (Loren et al., 2013; Oktay et al., 2018). Thus, it is important to inform patients that there is no significant delay in cancer treatment when choosing to preserve fertility, and that a prompt referral to a fertility specialist optimizes the lag time between diagnosis and cancer treatment commencement (Lee, Ozkavukcu, Heytens, Moy, & Oktay, 2010). Even though there is a lack of evidence, health professionals should also explain that there appears to be no increased risk of cancer recurrence after fertility preservation or/and pregnancy. Meeting with a social worker may also be beneficial to support decision-making process, to consider the financial resources and the associated costs of this procedure (Angarita et al., 2016; Loren et al., 2013).

Although these guidelines represent a step forward, additional efforts are needed to encourage clinicians to include infertility risk as part of the standard discussion for all cancer patients within reproductive years. This topic is not consistently addressed in clinical practice, despite the aforementioned ASCO recommendations (Angarita et al., 2016), and the provision of fertility preservation is still lacking. Improvements need to be made in the number of referrals from oncology to reproductive medicine specialists (Abdallah et al., 2017).

Health professionals' attitudes towards fertility preservation

There are many factors that impact patients' access to fertility preservation information. A few studies explored health professionals' concerns regarding these discussions and, although evidence suggested greater awareness, knowledge and willingness to discuss this subject with patients, many patients receive little information on this subject (Abdallah et al., 2017; Anderson et al., 2015; Angarita et al., 2016). A qualitative study, reported that clinicians voluntarily avoided this subject due to their beliefs that fertility would not be affected by treatment and that fertility preservation treatments are not effective or used by patients after cancer (Peddie et al., 2012). While still acknowledging the importance of fertility preservation for the patient's quality of life, only 13.5% of clinicians revealed to discuss the available options. High importance was given by almost all physicians (96%) to the quality of life after gonadotoxic treatment and to the provision of information about fertility preservation options (81%). However, when asked about the importance of infertility after cancer, a smaller percentage of physicians (59%) rated it as highly important (Louwe et al., 2013).

Several barriers were identified regarding communication in these situations, namely the clinician insufficient

updated knowledge regarding the available cryopreservation options, the lack of communication and access to reproductive medicine specialists, patients' characteristics (prognosis, age, parental status, marital status, financial capacity, sexual orientation, sexual maturity, HIV infection, and whether or not the patients initiate the conversation), the clinicians' perception of fertility as a minor issue, the fear of disease aggravation due to anticancer treatment delay, the availability of educational materials, as well as legal and ethical issues, such as the subsequent use of male gametes (Louwe et al., 2013; Peddie et al., 2012; Vindrola-Padros, Dyer, Cyrus, & Lubker, 2017).

These informational and communication barriers may prejudice and bias patient's decision-making processes and should be addressed with education on both health professionals and patients (Angarita et al., 2016). Future work should ensure that health care professionals receive adequate training on how to consent and discuss fertility risk and preservation options with young patients and their partners (Vindrola-Padros et al., 2017). Comprehensive counselling should also include related issues such as contraception use and health implications of early menopause (Benedict, Thom, & Kelvin, 2016).

Nevertheless, discussion of fertility prognosis and risk of recurrence at the time of diagnosis, may become an additional burden for clinicians. Communication skills should also be trained by consultation with other health providers, such as clinical psychologists and fertility specialists.

Patients' concerns and attitudes regarding risk of infertility

The percentage of female patients who are concerned about fertility issues, does not appear to be related to prior adherence to conservation methods, since the proportion of patients to whom this possibility was offered is still low (Angarita

et al., 2016; Armuand, Wettergren, Nilsson, Rodriguez-Wallberg, & Lampic, 2017; Banerjee & Tsiapali, 2016; Benedict et al., 2018; Shnorhavorian et al., 2015). Therefore, the percentage of women of childbearing age who are worried about their fertility after treatment is high and ranges between 57 and 66% (Perz, Ussher, & Gilbert, 2014). Being worried about the reproductive capability is one of the main causes of anxiety and psychological distress in this population (Howard-Anderson, Ganz, Bower, & Stanton, 2012). Risk of infertility is reportedly so emotionally draining as the cancer diagnosis itself. Nevertheless, it is usually considered a secondary worry, compared to mortality risk (Woodruff, 2010).

Several studies focused on exploring the sociodemographic and clinical characteristics related to these concerns, revealing that younger patients, highly educated, unmarried, professionally active, childless, who wish to have children and who previously had trouble getting pregnant before cancer, are the most concerned about the impact of anticancer treatments on fertility (Senkus et al., 2014). Young and childless women revealed a higher desire to become pregnant after breast cancer (76%) compared to women who already had children (31%) and who seemed to be more concerned about the possibility of recurrence (Senkus et al., 2014).

Regarding clinical variables, studies were mainly focused on time since diagnosis, cancer stage, disease dissemination and the quality of the information received, as factors correlated with infertility concerns and willingness to undergo fertility preservation procedures. Thus, when dealing with cancer diagnosis and, especially in a situation of an early-stage cancer, women revealed to be less concerned about fertility preservation, while being more focused on anticancer treatment and survival (Senkus et al., 2014).

Considering disease stage, studies hypothesized that higher cancer stages (and,

therefore, with higher risk of recurrence) are associated with greater acceptance of cancer treatments and its side effects (Senkus et al., 2014). Even so, fertility is important regardless of cancer stage and, therefore, the opportunity for preservation should be openly discussed with these patients as well (Loren et al., 2013; Oktay et al., 2018).

Regarding patients' attitudes towards fertility preservation, the European Organization for Research and Treatment of Cancer developed a study aiming to evaluate the proportion of participants who would not agree to chemotherapy if it affected their fertility. The authors found that, although survival and cure were the priority for young women with cancer, fertility preservation emerged as a matter of great importance. Results revealed that 59% of women from this study wished to have children (or more children), compared to 36% of women who do not want to have any more children for fear of recurrence. Women who had an easier acceptance of risk of infertility were women who already had children, did not intend to have more children, who were still waiting for the beginning of treatment (initial stage of the disease), and living in Western Europe (Senkus et al., 2014).

Studies also revealed that only 29% of the patients admitted that their concern about future fertility had an impact on treatment decision-making, 30% would postpone cancer treatment up to one month for fertility preservation (Tschudin et al., 2010), and only a small percentage of patients (<10%) would question the need for adjuvant treatment if their reproductive capability was at risk (Senkus et al., 2014).

In general, female patients revealed more positive than negative attitudes towards fertility preservation, which leads to the hypothesis that they are receptive to decide in favor of fertility preservation procedures, when correctly informed (Tschudin et al., 2010). Among males, those without a college degree, lacking private insurance and with children with less than

18 years, were more likely to not make fertility preservation arrangements (Shnorhavorian et al., 2015).

Patient information needs regarding fertility preservation

Research is also consistent in revealing that patients are generally uninformed about fertility preservation procedures, presenting low levels of literacy regarding this medical issue (Angarita et al., 2016; Banerjee & Tsiapali, 2016; Peddie et al., 2012). Regarding information, 43 to 62% of female cancer survivors reported important unmet information needs (Benedict et al., 2018), 26% felt that infertility risk was not well addressed by their doctors and revealed to be dissatisfied with the received information (Charif et al., 2015).

There seems to be a number of reasons why young women refrained from having these discussions with their clinicians, such as feeling overwhelmed with their cancer diagnosis or being unaware of the possible treatment impact on fertility (Loren et al., 2013). In consequence, 38% of women reported not making arrangements for fertility preservation because they were unaware of the options available, whereas 19% reported having financial and cost issues (Shnorhavorian et al., 2015).

Several studies focused on identifying the main barriers regarding the search for fertility conservation procedures. The results showed that one important barrier is the way information is delivered by oncologists and the emphasis they put on the urgency of starting anticancer treatments (Peddie et al., 2012). A reasonable percentage of patients (33.8%) revealed never discussing this subject with their husband, family, friends and/or health professionals because they felt that infertility risk was devalued and considered a minor issue when facing cancer (Tschudin et al., 2010). Additionally, patients older than 35 years and with children were less

likely to be informed about preservation options, and only 52% with chart-documented discussions regarding this subject, recalled having these conversations with their clinicians (Banerjee & Tsiapali, 2016). Consistently, studies pointed towards the need to inform patients about the anticancer treatments impact on fertility and on the existing preservation methods, regardless of their sociodemographic or clinical characteristics (Armuand, Wettergren, Rodriguez-Wallberg, & Lampix, 2015; Peddie et al., 2012; Tschudin et al., 2010).

Furthermore, some patients felt that there was a bias between the information that was delivered and the relevance the clinicians gave to the matter, while other patients revealed feeling pressured to start anticancer treatment and, therefore, not having enough time to think about the subject and make an informed decision (Dagan, Modiano-Gattegno, & Birenbaum-Carmeli, 2017). This could be the reflection of a judgment-bias regarding the clinicians' perceptions when considering the importance patients gave to their fertility after surviving cancer, which emphasizes the importance of how the information was delivered that may also impact the patient's decision-making processes (Louwe et al., 2013).

Patients comments on qualitative research, also highlighted the difficulty of considering fertility at the time of diagnosis. Hence, the need for more information seems to be less prominent at diagnosis, but increases during and after systemic anticancer treatments. After treatment, patients recognize the importance of discussing fertility prior to the beginning of the treatment (Peate, Meiser, Hickey, & Friedland, 2009) and revealed some disappointment regarding the quality and quantity of the information provided regarding their infertility risk and preservation options (Armuand et al., 2015).

Although fertility was not the priority at diagnosis, some women revealed

regret for not choosing to take preservation into consideration when it was possible. Research on decisional regret confirmed that women's perspectives on fertility changes over time, from the perception that procreation was not important to feeling regret over not having pursued conservation (Armund et al., 2017). These studies also revealed that pre-treatment fertility satisfactory counselling, leads to lower levels of post-treatment regret and better quality of life (Benedict et al., 2018). Lack of information regarding fertility risks can have important psychosocial consequences (Armund et al., 2015), and lead to patient's uncertainty, depression, anxiety, distress, anger and confusion (Assi et al., 2018; Charif et al., 2015).

More research is needed to understand what are the decision-making factors underlying fertility preservation. Research available is mostly cross-sectional and retrospective and there is a lack of longitudinal studies that may contribute to a better knowledge about patients' concerns, needs and attitudes regarding infertility risks, as well as how it evolves over time. Research should also focus on exploring individual risk factors for decision-regret in women with cancer in childbearing age and what are their future expectations regarding their reproducible capability and family plans. Only then, clinicians will have clear guidelines on how to educate patients about fertility preservation alerting for the possibility of mind changing processes, while encouraging the discussion of situations that might not seem urgent at the moment of diagnosis but will affect the long-term quality of life.

Impact of the risk of infertility in patient's quality of life

In non-clinical populations, infertility has been correlated with high levels of anxiety, depression, sadness, sense of loss, insomnia, lower self-esteem, threatened femininity, lower sexual and marital satisfaction, sense of life

interrupted, social avoidance, greater stigma, unsatisfying social relationships, and reduced quality of life, when compared to couples with no fertility problems (Pedro, 2018).

In oncology settings, recent studies indicated that the potential for fertility loss, may be more stressful than a cancer diagnosis itself (Assi et al., 2018). Infertility seems to be associated with high levels of distress, anxiety and depression (Howard-Anderson et al., 2012), and lower quality of life (Assi et al., 2018). It has also been identified as an experience marked by feelings of grief and loss, even in women who have fulfilled their family wishes before cancer (Peate et al., 2009). Especially young and childless women with breast cancer, revealed higher levels of psychological distress, lower self-esteem, uncertainty, relationship problems, more intrusive thoughts and more avoidance strategies (Armund et al., 2017; Assi et al., 2018), regardless of cancer site.

Nevertheless, it is important to mention that some studies also revealed that even women who already had children and who did not think about having more children after cancer, also face the risk of fertility loss as an emotionally draining experience (Peate et al., 2009). Even though 70% of patients revealed that the disease had no impact on their desire to have children, 13 to 15% stated that cancer diagnosis increased their desire to be mothers again and the value given to parenting (Armund et al., 2015).

Hence, infertility seems to increase the psychological distress associated with a cancer diagnosis, regardless of the patients' parental status, since it interferes with women's ability to decide about her life project regarding reproducibility and was imposed by the disease process, instead of her own decision-making. Therefore, even patients who did not intend to have children before the diagnosis, can feel the loss and the anger associated with infertility risk as a result of cancer and its treatment. Considering this, and since fertility is

usually described as an important part of the definition of being a woman, all patients should be informed about their infertility risk due to anticancer treatment, regardless of whether or not they have decided to have more children in the future.

In summary, few studies have evaluated the impact of fertility on female survivors' quality of life, including childhood cancer survivors. Little is known about the psychological impact of infertility risk during and after cancer treatment, or which individual variables can potentially protect or impact the quality of life in these situations. Based on studies conducted with infertile couples from non-clinical populations, one can understand that infertility has a great impact in several individual, relational and social domains and it becomes a threatening issue for quality of life, well-being, and satisfaction with life. Infertility in young women with breast cancer is another setback to their personal and relational development considered another great loss caused by cancer. Therefore, it is important to better understand the impact of infertility in patients' overall functioning, so that strategies can be developed to facilitate doctor/patient's communication processes and patients informed decision-making.

Conclusion

Several studies confirmed the cruciality of biological parenting for cancer patients of reproductive age (Armund et al., 2015; Assi et al., 2018; Benedict et al., 2018).

This review emphasized that the risk of infertility exceeds the diagnostic and clinical dimension of cancer, and is of great significance especially in female patients, since it endangers a fundamental life goal for most women: the opportunity of biological motherhood with several psychological, social, and spiritual implications for the couple and the family.

It is important that health professionals do not make assumptions

regarding fertility, since studies consistently indicate that patients, regardless of their clinical and sociodemographic characteristics, assess positively the possibility of discussing this issue with their oncologist. As a result, patients become more satisfied with the health care they received, regardless of choosing or not to preserve fertility (Peate et al., 2009).

Additionally, oncologist should consider that discussing infertility risk with patients does not implicate treatment adherence (Senkus et al., 2014) and, therefore, all the risks, options and benefits, should be clearly and carefully addressed, ensuring that the patient makes an informed decision (Peddie et al., 2012). Health care providers should discuss the possibility of infertility with adult patients and with parents of children diagnosed with cancer, as early as possible and address fertility preservation options and refer all potential interested patients to appropriate reproductive specialists. Although patients may be more focused on their diagnosis, oncologists should advise patients regarding potential fertility threats, present them with different options and prevent future regrets (Oktay et al., 2018).

Health professionals, while focusing on providing their patients quality care, should also encourage treatment adherence and fighting spirit, but also create opportunities for the patients to present its questions and concerns on all the subjects regarding their disease. Some attitudes of positive thinking and encouragement to proceed with treatments while facing their extensive side-effects, can be evaluated as forms of diminishing patients' concerns, inhibiting them to expose their true feelings and fears (Peddie et al., 2012).

Future studies should also identify an optimal approach to include fertility counselling and support resources into patients and survivor care programs. Infertility risk should also be included in informed consent about anticancer treatment (Loren et al., 2013; Vindrola-

Padros et al., 2017), especially before chemotherapy and endocrine therapy. Therefore, there is a need to develop informational materials (Bradford, Walker, Henney, Inglis, & Chan, 2018), clinical guidance and multidisciplinary consultations.

Research has already validated the existence of barriers in communication between patients and health professionals, regarding information on infertility risk and preservation procedures. Nevertheless, more information is needed on which individual and contextual factors might influence the patient's decision-making process.

To date, research focused on the psychological impact of infertility risk in cancer patients is still scarce. Studies are needed to assess and characterize young cancer patients concerns about their infertility risk, their expectations of fertility, their informational needs and attitudes towards childbearing during and after anticancer treatment.

Since the majority of the studies about oncofertility rely on small sample sizes and on qualitative methodologies, it should be noted the need to develop an instrument aiming to assess fertility concerns in young women with cancer to include in the health-related quality of life assessments in this population.

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