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Fertility and Fecundity After Chemotherapy for Childhood Cancer

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1. Introduction

In 2011, the regular increase in survival of childhood cancer (overall survival [OS] 72% at 10 years) (Berger 2006) suggests that one of every 850 adults in Europe has had pediatric cancer. As these children become adults, their concerns with possible long-term disease complications and risks associated with therapy received increase. Adverse effects of cancer therapies include disorders of the endocrine system, cardiac and pulmonary dysfunction, renal and hepatic impairment, secondary malignant disease, and psychosocial difficulties. Significant deliberation must also be given to the potential effects of a treatment regimen on the future fertility of pediatric patients with cancer. We review the literature regarding fertility and chemical risk factors for hypofertility in these patients to increase awareness of and avoid long-term clinical consequences of chemical therapies.

2. Gonadic toxicity

Gonadic toxicity results from systemic chemotherapy or irradiation of the spinal axis, pelvis, or entire body.

In boys, toxicity affects the somatic cells, i.e., the Sertoli and Leydig cells and germinal lineage. Sertoli cells assure the support, nutrition, and protection of germ cells, synthetizing numerous proteins, including inhibin and androgen-binding protein (ABP), and Leydig cells secrete testosterone. Chemotherapeutic toxicity primarily involves spermatogenesis, rise in follicle-stimulating hormone (FSH), and decline in inhibin.

Anti-Müllerian hormone (AMH) is the earliest Sertoli cell-specific protein expressed by the male gonad and is secreted by the testes from the eighth week of gestation and at high levels until puberty, when its decreasing production characterizes maturation of the Sertoli cells. The decline in AMH expression during puberty coincides with increased androgen secretion by Leydig cells and is considered a clear marker of the elevated intratesticular androgen concentration that inhibits AMH production by Sertoli cells at this time. The high level of AMH production before puberty allows its measurement to serve as a reliable marker for the presence of testicular tissue in childhood, when testosterone levels are very low.

Chemotherapy alone does not alter Leydig incapacity, as evidenced by a normal secretion of testosterone and declining levels of AMH during puberty. Puberty occurs normally even if involvement of the germinal lineage decreases testicular volume (A La Marca 2010).

Although female reproduction requires a functioning hypothalamic-pituitary-gonadal axis, ovaries, and uterus, reproductive potential in women is mainly limited by available oocytes. The process of oogenesis begins before birth with a peak in oocyte number (6 to 7 million) at 20 weeks' gestation followed by progressive atresia and drop in number of oocytes to one to 2 million at birth and 300,000 at puberty. Oocytes remain arrested as primordial follicles until puberty, a stage postulated to be less sensitive to gonadotoxins. At the initiation of puberty, a monthly cohort of follicles is recruited, one becomes dominant, and the others undergo atresia. Accelerated atresia coincides with a decrease in the quantity and quality of oocytes, raising the risk of infertility, aneuploidy, and spontaneous miscarriage. A rise in serum FSH often indicates accelerated atresia and impending ovarian failure. Before age 40 years, persistent FSH concentrations above 30 IU/L in the setting of amenorrhea, regardless of inciting events, suggest a diagnosis of premature ovarian failure (Rebar 2009).

Levels of anti-Müllerian hormone may represent the ovarian pool and could be a useful marker of ovarian reserve (A La Marca 2010). AMH is produced and secreted into the circulation by the gonads and can be measured in the serum of men and women. Nonsignificant variations in AMH levels have been reported throughout the menstrual cycle. In women, AMH levels seem to be unmodified under conditions in which endogenous gonadotropin release is subtantially diminished, such as during pregnancy, treatment with gonadotropin-releasing hormone (GnRH) agonist, and short-term oral contraceptive administration, indicating that non-cyclic FSH-independent ovarian activity persists even when pituitary FSH secretion is suppressed. However, sometimes damage to the ovarian reserve cannot predict ability to conceive.

Lie Fong and associates compared serum AMH levels in 185 adult female survivors of childhood cancer (excluding brain tumors) and 42 control subjects. Median follow-up was 18.1 years (range, 4.1 to 43.2 years). Median AMH concentrations were not significantly different between the analyzed cohort (1.7 μg/L) and controls (2.1 μg/L). However, in 27% of survivors, AMH levels were lower than the tenth percentile of normal values, and in 43%, they were lower than 1.4 μg/L, a previously established cut-off value for predicting ongoing pregnancy after assisted reproduction. AMH levels did not differ significantly in subgroups classified according to disease but were significantly lower in survivors who underwent 3 or more cycles of chemotherapy containing procarbazine than in controls (median 0.5 μg/L). AMH levels were also significantly lower in survivors who had been treated with abdominal or total body irradiation than in controls (median < 0.1 μg/L). AMH can be used to identify subgroups of survivors of childhood cancer who are at risk for decreased fertility or premature ovarian failure. In these survivors with high risk of hypofertility, the capacity for fertility preservation should be considered prior to starting assisted reproductive treatment because they may have a poor chance of achieving or maintaining pregnancy after treatment (Lie Fong 2009).

3. Which chemotherapies contribute to decline in fertility?

Alkylating agents, including cyclophosphamide, ifosfamide, chlormethine, busulfan, melphalan, procarbazine, and chlorambucil, are the primary chemotherapies that carry a high risk for gonadic dysfunction (Wallace 2005).

Boys frequently experience a passing rise in luteinizing hormone (LH) with azoospermia in the period just after receiving chemotherapy (2 to 8 years). In a series of patients affected by non-Hodgkin lymphomas, Pryzant describes an 83% recovery of spermatogenesis in patients receiving less than 9.5 g/m² of cyclophosphamide compared to 43% recovery in those receiving a higher dose (Pryzant 1993). A reduction of cyclophosphamide dose to less than 7.5 g/m² is associated with up to 70% conservation of fertility in survivors of Ewing's sarcoma.

A recent study including 6224 survivors aged 15 to 44 years who were not surgically sterile found a decline in fertility in men who had received childhood doses of procarbazine greater than 4.2 g/m² or cyclophosphamide greater than 9.3 g/m². Those who received cytarabine were more likely to ever sire a pregnancy than those who were not exposed to this agent. There is no clear explanation of this observation. The likelihood of siring a pregnancy was greater for men whose cancer was diagnosed and treated before age 4 years than those diagnosed between 15 and 20 years and did not differ for those diagnosed between 5 to 9 years or 10 to 14 years relative to those 15 to 20 years (Green 2010). Cyclophosphamide administration has been associated with impaired spermatogenesis after treatment of children for nonmalignant and malignant disease. Azoospermia has been reported after cumulative cyclophosphamide doses as low as 6 g/m² (Kenney 2001). In survivors of osteosarcoma, there is an implied risk of azoospermia from ifosfamide, with doses between 42 and 60 g/m² (Longhi 2003).

Byrne and colleagues evaluated fertility in male long-term survivors of acute lymphoblastic leukemia (ALL) diagnosed during childhood (Byrne 2004). Mean age at diagnosis was 10.9 years, and average age at interview was 22.8 years. Controls were siblings (average age, 24 years). Only 33% of male survivors had married or had a live-in relationship compared to 49% of male controls, and though the age in each group was similar for first fathering a pregnancy, fewer survivors than controls had become fathers. The relative risk (RR) for fertility was 0.80 for survivors aged 18 to 21 years when they first sired a pregnancy compared with sibling controls and 1.02 for survivors older than 21 years at the time they first sired a pregnancy. Men who received cranial radiotherapy (RT) without spinal RT before age 9 were less likely to become fathers than controls; their fertility was only 9% that of controls.

Ovarian function may be impaired after chemotherapy that includes an alkylating agent, such as nitrogen mustard, procarbazine, chlorambucil, or cyclophosphamide. The risk of ovarian failure appears to correlate directly with cumulative dose but inversely with age at exposure (Schilsky 1981, Andrieu 1983). Six cycles of combined nitrogen mustard, vincristine, procarbazine, and prednisone expose a patient to 8.4 g/m² of procarbazine and 72 mg/m² of nitrogen mustard. Such therapy carries a high risk of premature ovarian failure that may lead to precocious menopause. Green examined the fertility status of 5149 female survivors of childhood cancer aged 15 to 44 years who were not surgically sterile and noted that fertility decreased with increasing doses received of lomustine (CCNU) (from 360 mg/m²) or cyclophosphamide (from 3.7 g/m²). A low risk of pregnancy was also associated with increasing doses received of alkylating agents, such as those administered for Ewing's sarcoma (8.4 g/m² of cyclophosphamide and 63 g/m² of ifosfamide) (Green 2009). Chemotherapies administered before autologous stem cells that include high doses of alkylating agents, such as the busulfan (600 mg/m²) or melphalan, are a very important cause of premature ovarian failure (Teinturier 1998).

Byrne's group reported a significantly lower unadjusted fertility rate for female survivors of ALL than their siblings but could not demonstrate an effect of treatment with an alkylating agent or spinal irradiation on fertility rates (Byrne 2004).

4. Fecundity of survivors of childhood cancer

Fecundity, the capacity for producing offspring, is affected by various factors, including marital status, emotional disorders, endocrine or neurological disorders, and others.

A recent Italian study analyzes the marital (or living in couples) status of survivors of childhood cancer and compares it to that of the general Piedmontese population. At an average age of 28 years, 75% of survivors are not in couples, but the proportion is reversed after age 40 years, with 75% living in couples. On average, the wedding rate of survivors of childhood cancer is 32% lower than that of the general population for men and 18% lower for women. The discrepancy is very sharply marked for survivors of brain tumors, who are affected by endocrine and neurological complications as well as emotional disorders (Dama 2009).

For the Childhood Cancer Survivor Study, 20,720 patients were eligible for study, 17,561 questionnaires were sent (3159 lost to follow-up), and 3209 patients declined participation. At contact, 12,220 were aged 15 to 44 years (female, 5665; male, 6555). Five hundred and sixteen female survivors were surgically sterile, and 1372 indicated they had been pregnant 5 or more years after the date of their primary cancer diagnosis. Female survivors of the CCSS cohort were less likely than their sibling cohort to become pregnant (relative risk for survivors of ever being pregnant was 0.81 compared with female siblings). Pregnancy was more likely among those who had completed less than a high school education or were African American or married, findings that reflected the general population, or those in the youngest group at diagnosis (Green 2009).

We are conducting a study of fertility and quality of life of women treated in France for childhood cancer (except ALL) between 1948 and 1992 and sent 1261 survivors a self–assessment questionnaire that included an SF36 quality-of-life survey and questions on social outcomes, health, family, and fertility. Of 944 (75%) who answered, 489 had conceived at least one child, 29 adopted, and 94 could not bear a child despite their desire. There was no significant difference in quality of life between women with at least one child and women without children. By itself, the mental score of the SF36 appeared to correlate with growth deficiency, locomotive and psychological late effects, and age at diagnosis but did not correlate with initial tumor, gonadic deficiency, or fertility; the physical score correlated with neither fertility nor gonadic insufficiency. So, the SF36 findings seemed to indicate that the hypofertility experienced by patients treated for childhood cancer did not alter their quality of life. Future study could refine the psychological, social, and professional profile (personal data).

5. Knowledge of fertility?

The varied nature of gonadal insult after chemo- or radiotherapy often makes it difficult to predict whether treatment a patient is about to undergo will impair fertility. However, Wallace has proposed a classification of subfertility risk according to type of malignant

disease and associated treatment (Table 1) (Wallace 2005), and protocols for malignant disease are continually evolving to improve survival and reduce late effects, as seen, for example, in the intensification of treatment for ALL but less intensive management of Hodgkin disease over the last 10 years.

Low risk (< 20%)
Acute lymphoblastic leukemia
Wilm's tumor
Soft tissue sarcoma: stage I
Germ-cell tumors (with gonadal preservation and no radiotherapy)
Retinoblastoma
Brain tumor: surgery only, cranial irradiation < 24 Gy

Medium risk
Acute myeloblastic leukemia (difficult to quantify)
Hepatoblastoma
Osteosarcoma
Ewing's sarcoma nonmetastatic
Soft tissue sarcoma: stage II or III
Neuroblastoma
Non-Hodgkin lymphoma
Hodgkin's disease: alternating treatment
Brain tumor: craniospinal radiotherapy, cranial irradiation > 24 Gy

High risk (> 80%)
Whole-body irradiation
Localized radiotherapy: pelvic or testicular
Chemotherapy conditioning for bone marrow transplantation
Hodgkin's disease: treatment with alkylating drugs
Soft tissue sarcoma: stage IV (metastatic)
Ewing's sarcoma: metastatic

Table 1. Best assessment of risk of subfertility after current treatments for common cancers in childhood and adolescence (Wallace 2005)

A study in California (Zebrack 2004) noted that 59% of young adult survivors of childhood cancer from Los Angeles do not know whether they will be fertile. More than half indicate that neither their relatives nor doctors spoke to them of potential consequences of treatments received during the care of their cancer. Others received vague information concerning risks. Such findings suggest that health care providers who come into contact with long-term survivors of childhood cancer need to be prepared to provide them with accurate information about potential reproductive problems and risks for infertility based upon knowledge of their past treatment.

Van den Berg sent short questionnaires to parents of 159 male survivors of childhood cancer diagnosed and treated with chemotherapy in the Emma Children Hospital of Amsterdam (Van den Berg 2008), inquiring about year of birth, age at initial diagnosis, type of malignancy, and whether there was relapse. The remaining questions asked whether

information given at initial diagnosis included discussion of possible secondary infertility, if sperm was analyzed after treatment in pubertal boys, and if the parents expected their child to be infertile. Questionnaires were returned by 63%. Of these, 50% of parents recalled statements concerning an effect on fertility, 36% indicated that this had not been the case, and the remainder were unsure. Sperm analysis had been performed after treatment in 4 cases and semen collected prior to start of therapy in 14 cases; in 2 cases, the parent was uncertain in this regard. Nine percent of parents thought their son's infertility was a fact, 31% expected normal fertility, and 60% were uncertain.

Actual infertility influences not only procreation; even the suspicion of its risk profoundly affects body image, dating, and marriage (Schover 1999, Byrne 1989, Thaler-DeMers 2001, Zevon 1990). In long-term survivors of childhood cancer, at least 53% of men and 65% of women worry whether they can have children (Langeveld 2003). Limited knowledge of the effects of their treatment from inadequate processing of information given at diagnosis or failed memory of its content is a major contributing factor to these concerns. Parents are often an important source of information when a child suffers from a malignancy, and as children grow older, parents give them age-specific information. Data in this study indicate that despite the medical teams' certainty that parents were informed, half the parents could not recall receiving information concerning fertility. Care providers and/or parents might also withhold such information. Half the care providers stated that it is inappropriate to provide this information at the time consent is being given for treatment, considering it more important to offer information about fertility when therapy is finished (Goodwin 2007). The literature indicates that at least part of the poor recall of survivors of childhood cancer regarding issues of fertility is that the information was not provided by health care workers. Other contributing factors include the turmoil of unexpected events in the first weeks of illness in a case of childhood malignancy that often overloads parents with information on subjects with which they are unaccustomed and their withholding of information to shield their child from future burden or to avoid the child's reaction. It is highly recommended that medical providers check whether parents have received adequate information on their child's future fertility after they have had time to cope with the problems and emotions at initial diagnosis or relapse.

6. Fertility preservation

6.1 Male patients

Semen cryopreservation is an established and successful technique for men, and though its value has been shown in adolescent patients, it may be difficult to achieve. Treatment of malignant pediatric disease should be started as soon as possible after diagnosis, but teenagers at this early point in the disease process might be too distressed to discuss fertility and subsequently unlikely to produce a semen sample. Discussions should be dealt with sensitively in language understood by the patient. As well, it is important that sperm banking be practiced near pediatric oncology centers.

Boys sufficiently mature might produce semen samples by masturbation, or penile vibratory stimulation or rectal electrostimulation under anaesthetic can be considered if this method is not possible (Schmiegelow 1998). Alternatively, if spermatogenesis is established, sperm can be retrieved after testicular or epididymal aspiration.

Methods of storing sperm have improved significantly, and technological advances in assisted reproductive technology using intracytoplasmic sperm injection (ICSI) increase the likelihood of successful pregnancies using banked sperm.

Prepubertal boys pose additional challenges for fertility preservation because they cannot produce semen for cryopreservation. Germline cells of the prepubertal testes include spermatogonial stem cells, but mature spermatozoa are not yet present. A novel approach to circumvent this problem is cryopreserving the boy's testicular tissue. When he is ready to begin a family years after undergoing cancer treatment, the cryopreserved tissue is thawed and the banked germ cells reimplanted into the patient's testes to enable full maturation and reproductive potential (Brinster 2007). Unfortunately, a typical testicular biopsy contains insufficient numbers of stem cells to restore fertility, and a large supply of stem cells is required to ensure that no remaining cancer cells contaminate the transplanted cell population. Therefore, culturing methods must be developed to remove unwanted cancer cells and increase the number of biopsied stem cells to restore fertility through autotransplantation procedures. A novel approach is to employ a cryopreserved testicular sample to enrich for spermatogonial stem cells that are subsequently matured into viable spermatids *in vitro* through innovative culturing procedures. Use of this strategy could then achieve fertilization by ICSI (Ginsberg 2009).

6.2 Female patients

Oocyte cryopreservation is a feasible method of fertility preservation for young girls. Oocytes are fragile, and ovarian tissue consisting of germ cells can be removed and stored before gonadotoxic treatment. The ovarian cortex is utilized because it is rich in primordial follicles (Poirot 2002-2007). After the patient is cured, this tissue might be either returned to the patient via autotransplantation or matured *in vitro* to produce offspring by *in vitro* fertilization, similar to the technique proposed for male patients at this age. *In vitro* maturation is highly desirable because it obviates the concern of reimplanting cancer cells into the patient. Accordingly, the development of methodologies for obtaining human oocytes from primordial follicles is undergoing intensive laboratory investigation (Smitz 2010). However, ovarian transplantation may not be indicated in female patients with blood-borne malignancy because cancer cells circulating within the blood could remain in cryopreserved ovarian tissues (Dolmans 2010). Because ovarian biopsy is invasive and experimental, this option should only be considered for female patients at high risk of infertility. The most appropriate pediatric female candidates are patients undergoing stem cell transplantation, in whom there is a high likelihood of acute ovarian failure. In contrast, pediatric patients with cancer exposed to high doses of alkylating agents as part of their chemotherapy regimen, who often have a window of fertility following treatment and are more prone to premature ovarian failure, may have the opportunity as adults to undergo successful fertility preservation interventions.

Thus , ovarian cryopreservation, including transplantation, is now a clinical option available for children. Transplanted frozen/thawed tissue may be highly effective in restoring ovarian function and maintain function for prolonged periods of time. The many follicles present in children's ovaries could be used to induce puberty and possibly provide fertility later on. Although tissue can be transplanted to restore fertility, this method's efficacy is

limited and requires refinement. Results are encouraging for continued research efforts and may have far reaching possibilities that we must begin to address. Current research focuses on the possibility of hormonal protection of the gonad, long-term storage of testicular or ovarian material, and xenotransplantation into a host species. Transplanted material may subsequently be reintroduced into the patient, or gametes may be extracted for assisted reproductive techniques, such as *in vitro* fertilization.

7. Offspring among survivors of childhood cancer

7.1 Low birth weight in offspring after pelvic irradiation

One CCSS study included 1915 females who reported 4029 pregnancies (63% live births, 1% still4births, 15% miscarriages, 17% abortions, 4% unknown or in gestation). Pregnancy outcome did not differ significantly by treatment. There was a higher, but not statistically significant, risk of miscarriage among women whose ovaries were in the field of radiation therapy (RR = 1.86, $P = 0.14$), near the field (RR = 1.64, $P = 0.06$), or shielded (RR = 0.90, $P = 0.88$). The rate of live birth was not lower for patients treated with any particular chemotherapeutic agent. The offspring of patients who received pelvic irradiation were more likely to weigh less than 2500 g at birth (RR = 1.84, $P = 0.03$). This large study did not identify adverse pregnancy outcomes for female survivors treated with most chemotherapeutic agents but did indicate that the offspring of women who received pelvic irradiation are at risk for low birth weight (Green 2002).

7.2 No genetic anomalies among offspring

Drugs used to treat cancer are designed to interfere with DNA, cell division, and cellular metabolism, processes essential to embryogenesis and fetogenesis. A cohort study described by Byrne and associates (Byrne 1998) found genetic anomalies in 3.2% of 2198 offspring of survivors of childhood cancer compared to 3.1% in controls (4544 newborns). Similar results are reported in a Danish cohort (Winther 2004). Thus, there appear to be no genetic anomalies in offspring of survivors who underwent chemotherapy for childhood cancer.

7.3 Congenital anomalies among offspring

The large series described by Byrne (Byrne 1998) found congenital anomalies in 3.4% of 2198 offspring of childhood survivors compared to 3.1% in controls. Similarly, an international study (United States and Denmark) described by Boice and associates found no significant difference in relative risk of congenital anomalies among offspring of 25,000 survivors of childhood cancer who either fathered or gave birth to around 6000 children compared with their sibling controls (Boice 2003). Hawkins also reported only 46 congenital anomalies in 1033 (4.4%) newborns of cancer survivors, which is similar with the general population (Hawkins 1988).

However, an increased risk of congenital anomalies has been reported in the offspring of female survivors of cancer previously diagnosed with Wilms' tumor and treated with flank radiation. The mechanism underlying this risk has not been identified but may involve radiation damage to the female gamete (Green 2002 *JCO*)

7.4 No excess risk of cancer among offspring

In the Nordic cohort, including 14,652 survivors of cancer in childhood or adolescence diagnosed since the 1940s and 1950s, only 22 sporadic cancers, excluding retinoblastoma (17 cases) and other hereditary cancers, were observed among 5847 offspring. The standardized incidence ratio is 1.3 (95% confidence interval [CI], 0.8 to 2.0). No neoplasms were observed among the children of survivors of leukemia, neuroblastoma, or hepatic tumors. The overall standardized ratio for nonretinoblastoma neoplasms was 3.9 (95% CI, 2.1 to 6.7) for offspring whose parents were younger than 10 years at diagnosis and 1.1 (95% CI, 0.6 to 1.8) for those with parents diagnosed at age 10 or older. All but one offspring with cancer were born at least 8 years after cancer was diagnosed in their mother (Sankila 1998).

There seems to be no increase in childhood malignancies in offspring of survivors, with the exception of cancers arising as a result of inherited syndromes, including familial adenomatous polyposis, hereditary nonpolyposis colon cancer, retinoblastoma, Li-Fraumeni syndrome, and others.

7.5 No modification of sex ratio

Some researchers have assessed the sex ratio of fetuses born to cancer survivors after treatment compared with the general population and noted no difference, ensuring that cancer treatment does not increase incidence of X-linked mutations (Winther 2003)

8. Conclusion

Infertility is an important issue arising as a late effect of childhood cancer treatment and should be discussed at initial cancer diagnosis if therapy may carry some risk. Although the topic may be difficult for parents, it is necessary to consider some method of protecting fertility at an early stage, even in young children. Although it is very difficult to predict fertility after treatment, there is much interest in potential markers of gonadal damage that can be used in adolescents and young adults.

Beyond the possible precautionary measures in assessing issues surrounding fertility in survivors of childhood cancer, it is necessary to review the history of the patient's disease and treatment regimen, clarifying chemotherapies, surgeries, and irradiation, and biologic markers may also be measured (FSH, testosterone, estradiol, AMH). Knowledge of these data will elucidate how to care better for the patient, and if there is a risk to fertility, a couple can be referred for consultation with a health center for assisted reproduction.

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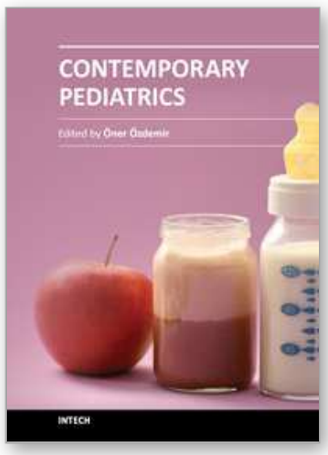

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