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Commentary on "Parental Attitudes Toward Fertility Preservation in Boys with Cancer: Context of Different Risk Levels of Infertility and Success Rates of Fertility Restoration," Sadri-Ardekani et al. (2013). *Fertil Steril* 99: 796-802.

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ABSTRACT

Cancer survival rates have increased dramatically in recent decades. Until better cancer therapies emerge, infertility will remain a common side effect of cancer therapy. Infertility therapies have likewise flourished in recent decades, but unfortunately the science of infertility has been relatively slow to infiltrate the oncology world. Parents of children with cancer are interested in preventing and/or preserving their children's fertility. But do they know what their options are? Do they even know infertility is a risk? The answer to both, sadly, is often no. However, now that we know the majority of parents would agree to fertility preservation techniques, we may confidently proceed with appropriate clinical trials.

Cancer survival rates have increased dramatically in recent decades. Until better cancer therapies emerge, infertility will remain a common side effect of cancer therapy. Infertility therapies have likewise flourished in recent decades, but unfortunately the science of infertility has been relatively slow to infiltrate the oncology world. This dichotomy may in part be attributed to several reasons: Most cancers occur in adults past their peak child-bearing years, sperm banking has been available and successful for decades, and in vitro fertilization and other assistive reproductive technologies have been successfully used since the late 1970s [1].

However, thousands of prepubertal children are diagnosed with cancer every year worldwide, and for them these reproductive technologies are not realistic options. For females, eggs are present at birth in the ovaries and can be harvested, although it is technically challenging and rarely done [2]. In prepubertal boys, sperm are not made until puberty progresses through an appropriate stage, typically Tanner stage III or IV development, which for most males occurs around the age of 12 or 13. For those boys, sperm may be obtainable by masturbation or electro-ejaculation. (Despite the misleading name, electro-ejaculation is not painful.)

Parents of children with cancer are interested in preventing and/or preserving their children's fertility. But do they know what their options are? Do they even know infertility is a risk? The answer to both, sadly, is often no.

Sperm banking for postpubertal males is routinely offered at some oncology centers and rarely at others. The diagnosis of cancer is usually followed by a flurry of tests, operations, and the initiation of therapy. In children and adolescents, there is often very little time between diagnosis and the start of chemotherapy. Although well known to pediatric oncologists, the risks of infertility are often not explicitly shared with patients and their parents. There are likely several reasons for this, including lack of certainty and individual variations. But the primary reason probably boils down to this misconception: Infertility is a price one may have to pay to be cured.

KEYWORDS: Cancer survival, fertility preservation, pediatric cancer

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But does it have to be?

For prepubertal boys, it may be possible in the future to restore or improve fertility by re-implanting stored spermatogonial stem cells (SSCs) back into the testes after cancer therapy and sexual maturity have been completed. Although animal models show promise in different species [3], including non-human primates [4], human trials have not yet been conducted. The first step in this therapy would involve testicular biopsy and cryopreservation, ideally before the boy has been exposed to any chemotherapy agents that could harm his SSCs. Before this technology can move forward, it is imperative to know if it would be accepted by families.

Would parents agree to testicular biopsy? When testicular biopsy is coupled with sperm banking via masturbation or electro-ejaculation, about two-thirds of parents would agree with fertility preservation interventions if the chance of infertility or successful fertility restoration is at least 80%. Surprisingly, about one-third of parents would agree, even if the chance of infertility is low (< 20%) and even if the chance of successful restoration of fertility is low (< 20%) [5]. Therefore, all parents should be counseled about the risks of infertility and available fertility preservation options.

A parent's primary objection in this study is that fertility preservation interventions may harm their son. This is a rational concern given the sensitivity to even minor trauma of the testicles. But in fact testicular biopsy is easy and safe, with relatively few short- or long-term side effects [6]. A lesser parental concern is that the boy should decide such matters for himself. Importantly, the majority of parents surveyed indicated a willingness to donate up to one-third of the testicular tissue for research. Such research is crucial to facilitate clinical application (i.e., SSC autotransplantation in humans) as soon as possible.

This report is limited by its retrospective nature and limitation to a single country (Iran); however, the acceptance rate for different fertility preservation options in this study was in the same range as earlier studies in the Netherlands and the USA [7,8]. The message is clear: Most parents of pediatric oncology patients are under-informed about fertility implications of cancer therapy, and most would want their son to undergo fertility preservation. Predictably, increased infertility risk and increased theoretical success rates both independently increase parent interest.

Could testicular biopsy tissue contain cancer cells? This is a particular concern for patients with leukemia, in whom occult testicular involvement is relatively common (approximately 20%). Among others, a recent report shows the effectiveness of flow cytometry for separating out malignant cells from SSCs, suggesting this problem can be avoided [9].

Is there time between diagnosis and the initiation of chemotherapy? For most patients the answer is yes. The majority of patients undergo surgery for tumor biopsy/resection and/or other procedures such as central-line placement, bone marrow aspirate/biopsy, or lumbar puncture. With careful planning and coordination, a testicular biopsy (or ejaculation via masturbation or electro-ejaculation) can be safely completed in most cases.

So what are the next steps? Now that we know the majority of parents would agree to fertility preservation techniques, we may confidently proceed with appropriate clinical trials. In addition, it is imperative that education continues in this arena, not only to parents but also to health-care professionals, and most importantly pediatric oncologists who are crucial to the success of such trials.

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