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MEN'S HEALTH (A DABAJA, SECTION EDITOR)

Non-oncologic Indications for Male Fertility Preservation

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Abstract

Purpose of Review To explore non-oncologic indications for male fertility preservation.

Recent Findings Common scenarios in which male fertility could be irreversibly compromised include autoimmune conditions requiring treatment with cyclophosphamide, gender dysphoria prior to starting hormone therapy, military deployment, and critical illness. Fertility preservation should be considered with particular attention to the timing and logistics specific to each scenario.

Summary Recognition and familiarity with such situations will help physicians provide better counseling to patients and their families, improve the quality of decision-making, and ultimately reduce missed opportunities and regret.

Keywords Male fertility preservation · Cyclophosphamide · Gender dysphoria · Postmortem sperm retrieval · Military deployment

Introduction

As the technology for assisted reproduction has improved over the last few decades, the cryopreservation of sperm has become an effective and widely used method for fertility preservation for men. While most commonly used in cancer patients undergoing gonadotoxic chemotherapy, the indications for fertility preservation in men have expanded beyond the oncologic setting to include autoimmune conditions, gender dysphoria, critical illness, and even military deployment. Early recognition of the potential need for fertility preservation is critical in order to provide patients adequate counseling and time for informed decision-making. Here, we review current practice guidelines and recent literature in each of these situations.

This article is part of the Topical Collection on *Men's Health*

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Autoimmune Conditions Requiring Cyclophosphamide

Severe manifestations of autoimmune conditions require treatment with medications that have a negative impact on fertility. These conditions are relatively common when compared to oncologic indications for gonadotoxic medications: the prevalence of systemic lupus erythematosus (SLE), for example, was estimated to be approximately 24 per 100,000 people in 2003 [1]; the prevalence of testicular cancer around the same time was estimated to be approximately 7 per 100,000 people [2]. Non-oncologic conditions currently only account for approximately 10% of the overall demand for fertility preservation [3], however. This may be in part due to either less frequent counseling or recognition of need for these patients compared with patients with malignant diseases.

Common gonadotoxic medications used for such benign indications include cyclophosphamide, methotrexate, mycophenolate mofetil, and mTOR inhibitors. From a general reproductive standpoint, it is widely accepted that men who are taking any of these medications should use contraception as many of these are either category D or category X teratogens. Cyclophosphamide, however, is the only medication for which the evidence to support the use of fertility preservation is strongly supported by clinical studies [4]. We will thus focus our discussion on considerations for patients initiating treatment with cyclophosphamide.

Cyclophosphamide generally affects spermatogenesis via several mechanisms. As an alkylating agent, it causes DNA damage by cross-linking DNA strands, which interferes with germ cell division and differentiation [5]. It also induces oxidative stress and impairs the function of both Sertoli cells and Leydig cells [6]. Men who receive cyclophosphamide have been found to have low levels of serum testosterone, luteinizing hormone, and follicular-stimulating hormone. In terms of teratogenicity, studies show the risk of producing genetically abnormal sperm is greatest approximately 1–2 weeks after the end of therapy [7]; current guidelines recommend waiting 6–12 months after completion of therapy before sperm are “safe” for use in reproduction. Animal models, however, have shown that exposure can lead to the permanent accumulation of mutations in the germline and lead to transgenerational teratogenicity [8•]. While, we are not aware of any studies demonstrating a long-term effect in humans, it remains an important concern and is another strong argument for considering sperm cryopreservation prior to initiating treatment.

From a semen quality standpoint, exposure to cyclophosphamide leads to outcomes ranging from decreased sperm motility [9] to azoospermia [10] depending on the length of treatment and dose administrated. In some conditions such as SLE, this deleterious effect may be compounded by a baseline sperm dysfunction [9]. There have been cases reported of permanent azoospermia after treatment with cyclophosphamide [11, 12].

It is clear that all men of reproductive age should be offered fertility preservation counseling prior to the start of cyclophosphamide treatment. The timing of treatment presents a major obstacle, however. Since it is usually used in the acute setting to reverse end-organ damage such as renal failure, most patients are in an inpatient setting and often have very little time to receive adequate counseling prior to initiating treatment. Furthermore, the practical aspects of sperm retrieval in this setting could potentially delay treatment for their primary medical problem. Anticipating the need for fertility preservation prior to this phase of care will enable patients and their physicians the time to plan appropriately.

In our experience, it is not uncommon to receive a consultation request for sperm cryopreservation several weeks after patients have already initiated treatment. This presents a difficult scenario: the critical question in this case is whether semen specimens can be used for cryopreservation even after systemic exposure to cyclophosphamide. It is theoretically possible that the majority of sperm are “normal” since the sperm most likely to be altered are still undergoing spermatogenesis, which is thought to take approximately 74 days. Whether to cryopreserve within this window in practice, however, is unclear. At our institution, the policy is not to cryopreserve if there has been any exposure at all to chemotherapeutic medications in the preceding 3 months given the potential increase in DNA fragmentation and a theoretical increase in risk of birth defects using this sperm and a lower rate of sperm survival with cryopreservation after exposure to chemotherapy. However, some institutions do offer preservation of these samples for use as a last resort in the event that patients become irreversibly azoospermic.

It should be mentioned that efforts are ongoing to develop pharmacologic agents to mitigate the effect of cyclophosphamide on spermatogenesis. Such agents include *Tribulus terrestris* extract, vitamin C, pumpkin seed extract, and ginger extract [13–15]. Studies in animal models have demonstrated improvement in semen and histologic parameters when these agents are co-administered with cyclophosphamide, suggesting a protective effect. More investigation is necessary to validate human use and these interventions are not currently considered as part of standard clinical care.

Transgender Women Undergoing Feminizing Hormone Therapy

The number patients seeking treatment for gender dysphoria is increasing in many countries, likely due to social, cultural, and political reforms that have led to increased awareness and acceptance of transgenderism [16]. In medicine, gender-affirming treatments such as feminizing or masculinizing hormones and genital surgery are now routinely offered as the standard of care. These interventions can have significant and irreversible effects on fertility; since surveys have shown that more than half of transgender patients desire future children [17, 18], fertility preservation should be discussed with all patients before initiating treatment. This is particularly important for patients undergoing sterilizing genital surgery. Here, we will focus on considerations for sperm cryopreservation in transgender women (male-to-female) undergoing hormone therapy.

Feminizing hormone therapy (FHT) is the mainstay of treatment for transgender women. The general goals of FHT are to suppress testosterone production, block the effect of testosterone, and elevate estrogen levels [19], although pharmacologic regimens can vary widely in practice. Typical combinations often include some form of estrogen, which suppresses the hypothalamic-pituitary-gonadal axis and inhibits testicular testosterone secretion; spironolactone, which at high doses acts as both an androgen receptor antagonist and gonadal testosterone production inhibitor; 5-alpha reductase inhibitors, which block the conversion of testosterone to dihydrotestosterone; and gonadotropin-releasing hormone analogs such as leuprolide which inhibits the release of luteinizing hormone and follicle-stimulating hormone from the pituitary gland.

Several studies have demonstrated a dramatic effect of FHT on spermatogenesis. An analysis of testicular sperm production in patients undergoing gender-affirming orchiectomy showed that only 4% of transgender women had microscopic evidence of normal spermatogenesis, whereas 79% had no microscopic evidence of any spermatogenesis [20]. It should be noted that some patients in this cohort did not report exposure to FHT. A more recent retrospective study of transgender women undergoing sperm cryopreservation demonstrated that semen parameters in patients using FHT compared to those who never used FHT are notable for decreased motility (15.6% vs 51.5%), concentration (2.4% vs 63.6%), volume (0.9 mL vs 2.7 mL), and total motile count (0.2 million vs 63.2 million) [21•]. This study also showed that while the sperm counts can recover after withdrawal of FHT, a history of exposure still has deleterious effects on semen quality compared to FHT-naïve patients.

Fertility counseling prior in transgender patients is thus important to optimize timing of fertility preservation prior to FHT and to establish realistic expectations for future options should cryopreservation be deferred. Whereas sperm banking may be relatively straightforward for FHT-naïve patients, those who have initiated treatment and have poor semen parameters could require invasive sperm extraction techniques [22]. An additional consequence of having fewer viable sperm would be limiting reproductive options to in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) versus the much less costly option of intrauterine insemination (IUI). Alternatively, discontinuation of FHT altogether for a period of time remains an option, although many transgender women experience severe dysphoria and re-virilization upon stopping these medications.

Military Deployment

There are more than one million active duty military personnel in the USA, the majority of which is comprised of men of reproductive age. Active duty and deployment in particular pose significant barriers and risks to reproduction. Considerations include delays in family planning, physical separation of soldiers from spouses, and the risk of genital trauma that could result in infertility. Cryopreservation of sperm prior to military deployment thus warrants further discussion and investigation not only from a medical standpoint but also from a policy standpoint.

According to Department of Defense data in 2010, the average age of military personnel deployed in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) was 33.4, with 45% between the ages of 25 and 34. Approximately 60% were married at the time of deployment, and 51% did not have children [23]. The average length of each deployment ranged from 4.5 months in the Air Force to 9.4 months in the Army, and those with multiple deployments often accumulated up to 2 years of total deployment time. The nature of modern warfare involving improvised explosive devices (IEDs) has increased the severity of genitourinary injuries. During OIF alone, there were 1300 genitourinary injuries documented, of which 33% were to the testes and 31% to the penis [24].

Tricare, which provides healthcare benefits to military personnel, currently does not offer routine sperm cryopreservation to active military personnel aside from a few exceptions (e.g., those who have sustained fertility-compromising genitourinary injuries). In 2016, the "Force of the Future" budget proposal sought to incorporate the option of sperm cryopreservation prior to deployment as part of its basic health plan. This would have been offered to all military personnel under the age of 39 and would have covered a cryopreservation period for up to 2 years. However, the proposal fell through in 2017 and no efforts have been made to reinitiate it. According to the American Society for Reproductive Medicine, the major obstacle is conservative ideological opposition to IVF associated with sperm cryopreservation.

Military personnel who wish to undergo sperm cryopreservation prior to deployment thus need to do so through non-government facilities. Although there are some private programs that offer military discounts, very little data exist on how often service members are able to pursue these opportunities out-of-pocket. One single-institution review out of Texas A&M reported that 5.5% of banked samples were for active military personnel, although the primary indication for banking was reported to be pre-existing infertility in couples who happened to have one partner in military duty [25].

Our opinion is that fertility preservation should be discussed prior to deployment. Even if cryopreservation services are not offered within government healthcare facilities, military personnel should be made aware of the options and be given the opportunity to pursue them should they choose to do so. The data are sparse in this area from a health services standpoint, so it will be interesting to study future trends in the utilization of fertility preservation in the military, especially if routine counseling becomes standard of care prior to deployment.

Critically Ill Patients and Posthumous Sperm Retrieval

An estimated 4 million intensive care unit admissions occur yearly in the USA, with mortality rates ranging from 8 to 19%, or 400–500,000 death annually [26–28].

According to the CDC, 6–7% of the men who died in the hospital between 2000 and 2010 were under 45 and 24–27% under 65 [29]. According to the CDC, the leading cause of death in men of reproductive age is traumatic injury, closely followed by malignant neoplasms. The topic of fertility preservation is often not discussed with these patients, in part due to the sensitive nature of perimortem and posthumous sperm retrieval (PSR), which is possible 24–36 h after death. Although PSR has been performed since 1980 [30], it has been fraught with myriad controversies involving conflicting moral, scientific, and religious values across communities and cultures. The major issues include the problem of consent, ownership of gametes before and after death, welfare of any potential offspring, and whether PSR should be performed at all.

When this question does arise, as it does a handful of times annually at our institution, physicians have a responsibility to understand the ethical and legal issues to provide effective and timely counseling to these patients and their loved ones. These issues will be explored with the help of the following three case scenarios.

Example 1 *A 35-year-old man is admitted to the ICU for stage IV rectal cancer with bowel perforation. He is not a candidate definitive therapy. He is not yet intubated and has decision-making capacity. He and his wife desire children.*

The main issue here is related to the uncertainty around the patient's survival, and whether procreation after one of the partners' death should be allowed. This is generally a conversation regarding welfare of the offspring, which tends to be a matter of personal opinion rather than ethical righteousness. In fact, no laws exist (at least not in the USA) that forbid the use of assisted reproductive technology (ART) by a single parent, or that strictly forbid using gametes of a deceased donor. This scenario is not so different from a single woman requesting the services of a fertility clinic to achieve pregnancy after all. While certain clinics or physicians may decline to perform the procedure for personal reasons, a single or widowed woman is ultimately entitled to the same rights to ARTs as other couples. Our recommendation in this case would be to discuss gamete retrieval methods and use of gametes with the patient's spouse as part of an advance directive (AD).

Example 2 *A 29-year-old man is in a persistent vegetative state after suffering head trauma in a high-speed motorcycle accident. The family wants to explore fertility preservation options.*

According to the American Society for Reproductive Medicine (ASRM), decisions around the use of gametes belong to the individual they came from [31], unless he or she has consciously given up those rights (e.g., sperm donation). Thus, procreation without the gamete owner's consent can be considered to be in violation of that individual's autonomy. In an ideal situation, a patient who loses consciousness will have previously written an advance directive that includes his beliefs around the retrieval and use of his sperm in case of incapacitation or death. Unfortunately, fewer than 20% of adults of reproductive age discuss AD [32]. In the absence of an advance directive, the opinion among many academic centers is that "the decision to perform PSR must be based on the deceased man's previous attitudes as interpreted by the surviving partner, and at times extended family members" [33•]. Unfortunately, this is open to broad interpretation; consultation with the hospital ethics board may thus be warranted in most cases.

Example 3 *A 33-year-old man sustains multiple gunshot wounds to the chest and abdomen and dies in the operating room. His gametes are still viable and his fiancée desires sperm retrieval. Consent was not obtained before death, and the patient does not have an advance directive.*

Some countries such as France and Germany have strict laws against PSR regardless of consent, while others allow it under certain conditions. In Israel, for example, it is assumed that a man in a "loving relationship" would consent to the procedure [34]. In the UK, the procedure is allowed only if consent was provided prior to death [35]. The rules are more vague in the USA: PSR is freely allowed if consent was provided prior to death; when consent was not explicitly given, the ASRM recommends that "in the absence of written documentation from the decedent, programs open to considering requests for posthumous gamete procurement or reproduction should only do so when such requests are initiated by the surviving spouse or life partner" [36]. Such cases are not always straightforward, and they are often handled by the physicians involved in the care of the patients, by the hospital's ethics committee, and by the legal system. Strict guidelines do not currently exist, and a case-by-case discussion is typically the course of action followed.

Overall, fertility preservation in the setting of acute illness and death challenge the physician to think about two separate questions. On the one hand, can gametes be ethically removed from a deceased patient? On the other, should those gametes be used for procreation? Ultimately, in the absence of explicit consent, no healthcare provider is obligated to comply with such requests, but the option should be considered and discussed with the parties involved. A multidisciplinary approach that involves consulting fertility specialists and the hospital ethics committee is encouraged.

Compliance with Ethical Standards

Conflict of Interest Heiko Yang, Joris Ramstein, and James Smith each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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