Fertility Preservation Before Deployment: Oocyte and Sperm Freezing in Members of the Active Duty Military

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Abstract

Active duty military service and deployment has the potential to compromise fertility through combat-related genitourinary injury, gonadotoxic exposures, and physical separation from a partner. Despite a growing interest among the military community as well as promising efficacy and safety data, fertility preservation remains an uncovered benefit for active duty soldiers. In 2016, the Pentagon proposed a program that would cover oocyte and sperm cryopreservation for any member of the active duty military desiring its use. Regrettably, that funding was not secured and predeployment fertility preservation remains an out-of-pocket expense. Today, advocacy groups, non-for-profit organizations, and physicians remain vigilant in their attempts to drive another government initiative through Congress. While activism continues, it is important to stress the value of fertility preservation counseling in soldiers' predeployment preparation and military family planning.

Keywords
- fertility preservation
- military
- deployment

There are a multitude of factors that have the ability to influence the reproductive capacity of a man or a woman. These include various medical conditions or syndromes, gonadotoxic therapy, gonadal injury, or age-related fertility decline. Over the last decade, there has been an increase in utilization of fertility preservation services for nonmedical indications in both men and women, including an elective interest in delayed childbearing.[1] Though pregnancy outcome data are continuing to evolve as more patients return to use their stored gametes, the reports that are currently available for both cryopreserved oocytes and sperm are encouraging.[2–4]

The American Society of Clinical Oncology (ASCO) and the American Society for Reproductive Medicine (ASRM) stress the importance of discussing fertility preservation in patients undergoing gonadotoxic therapies.[5,6] Despite these guidelines and a strong desire by patients to be informed of the fertility preservation options available, referrals to reproductive specialists are not part of routine practice in all centers.[5] With fertility preservation indications extending beyond the walls of oncology, it is likely that providers in other disciplines also fall short in recommending fertility preservation counseling to those who may be at risk for fertility compromise.

Military deployment presents a multifaceted threat to both male and female fertility due to the reproductive delay posed by physical separation from a partner and the risk of gonadal injury or gonadotoxic exposure while in combat.[7] Though few options exist for gamete retrieval in injured soldiers, available techniques are suboptimal when compared with elective fertility preservation in healthy, uninjured gonads.[8,9] The Department of Veterans Affairs (VA) provides financial assistance for assisted reproductive technology (ART), including gamete cryopreservation, for veterans with a service-connected disability or medical conditions that render them unable to naturally reproduce.[10] Conversely, the U.S. Department of Defense (DoD)

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does not provide coverage for ART or cryopreservation of gametes for active duty men and women in any scenario, including prior to deployment. Despite an attempted initiative in 2016, limited progress has been made in securing funds to cover these services. As it currently stands, the option to pursue and finance predeployment fertility preservation is a burden borne by the soldier. As fertility preservation techniques become increasingly effective and rates of genitourinary (GU) injury sustained during deployment remain relatively high, strong consideration should be given to providing referrals for fertility preservation counseling in active duty military members predeployment. This article will summarize the available techniques and success rates for male and female fertility preservation; provide an overview of the fertility challenges faced by those in active duty; and comprehensively review the past, present, and hopeful future of U.S. policies regarding fertility preservation as a covered service for members of the active duty military.

Fertility Preservation: Overview of Techniques, Success Rates, and Utilization

Female Fertility Preservation

A woman's reproductive lifespan is entirely dependent on the number of oocytes with which she is born. A decline in oocyte quantity and quality occurs gradually, but begins to accelerate after the age of 32 and even more quickly after the age of 37.[11] Historically, fertility preservation techniques were primarily sought by women undergoing gonadotoxic therapy as a means of safeguarding their reproductive potential for use following treatment. As the efficacy of oocyte cryopreservation began to improve, there was a parallel rise in the population of women pursuing treatment to delay childbearing until later in their reproductive years. Elective fertility preservation, with the goal of circumventing this natural ovarian aging process, now outpaces medically indicated treatment in terms of the number of cycles performed annually in the United States.[12–14]

The preferred technique for fertility preservation in females involves the cryopreservation of metaphase II oocytes obtained through the process of controlled ovarian stimulation. If needed for procreation, these oocytes are later thawed and inseminated to create embryos for use during an in vitro fertilization (IVF) cycle. Oocyte cryopreservation was considered an experimental therapy until 2012 when ASRM issued a document which effectively lifted its experimental label.[12] Prior to that time, cryopreservation of embryos obtained through IVF was the only nonexperimental method to preserve a woman's fertility. As embryo cryopreservation is limited to those women with a male partner or a willingness to inseminate her eggs with donor sperm, oocyte cryopreservation has opened avenues to more women seeking cryopreservation for both elective and nonelective indications.[15] Other techniques for female fertility preservation such as in vitro maturation of immature oocytes and ovarian tissue cryopreservation are still considered experimental, but are available at some centers for prepubertal girls or women with aggressive or hormone-sensitive malignancies who cannot undergo standard fertility preservation methods.[1] Ovarian suppression with gonadotropin-releasing hormone agonists has been demonstrated to reduce the rate of chemotherapy-induced premature ovarian insufficiency, but does not unequivocally guarantee future pregnancy success.[16]

Oocyte cryopreservation was historically performed using slow-freezing techniques. Slow-freezing, developed in the 1970s, utilizes a programmable device which cools the tissue at a slow rate (0.3–2.0°C/minute), thereby maximizing cellular dehydration and minimizing the formation of intracellular ice crystals that could compromise tissue survival. An alternative technique called vitrification has been used in other fields at least as long as slow-freezing, but was not applied successfully to human oocytes until the last decade. Vitrification allows for ultra-rapid and effective cooling of tissue (>20,000°C/minute) through the use of high concentrations of cryoprotectants and high temperature gradients.[17] Though slow-freezing protocols have improved since their inception, recent data demonstrates that vitrification of oocytes results in higher post-thaw survival, embryonic development, and pregnancy rates when compared with slow-freezing.[18–22]

The performance of cryopreserved oocytes continues to improve as centers refine and perfect their cryopreservation and thaw methods.[12] A recent meta-analysis of five randomized controlled trials demonstrated that fertilization and pregnancy rates were similar between fresh and vitrified/warmed oocytes used for IVF with intracytoplasmic sperm injection (ICSI).[23] The largest randomized controlled trial comparing fresh versus vitrified donor oocytes found that both groups were statistically similar in terms of fertilization rates as well as implantation and clinical pregnancy rates per embryo transferred (74, 61, and 55%, respectively).[24] Due to declining oocyte quality with increasing age, pregnancy rates will vary based on the age at which the oocytes were retrieved. Doyle et al estimated probabilities of live birth in patients who pursued elective oocyte cryopreservation according to the number of mature oocytes retrieved and age at the time of retrieval. For women aged <38, cryopreserving 15 to 20 mature oocytes gave an approximate 70 to 80% chance of at least one future live birth. Comparatively, women aged 38 to 40 cryopreserving 25 to 30 mature oocytes led to an estimated 65 to 75% chance of at least one future live birth.[2] Given that oocyte quantity also declines with age, obtaining the recommended number of oocytes to maximize chances of future live birth may not always be feasible. Additionally, as the majority of published outcome data comes from large centers proficient in oocyte cryopreservation and thaw techniques, the results may not be entirely generalizable to all clinics.

Oocyte cryopreservation is widely accepted by the public across a variety of freezing indications. Results of a national internet survey of both men and women demonstrated that 89% of respondents supported oocyte cryopreservation for cancer, 72% for delayed childbearing, and 63% for being unpartnered.[25] Another survey study of U.S. women pursuing elective cryopreservation reported women felt they had improved their reproductive future and felt empowered by the process.[26] Furthermore, studies evaluating the cost-effectiveness of elective egg freezing demonstrated reduced live

birth costs when eggs were frozen prior to age 38.[27] Despite its public support and cost-effectiveness, it is often cost prohibitive. A cross-sectional survey study of U.S. women of childbearing age demonstrated that those interested in egg freezing would only be willing to pay $3,811.55, which is significantly less than what clinics standardly charge.[28] Even with some large companies funding elective egg freezing for their employees and six U.S. states passing laws covering fertility preservation for patients at risk for iatrogenic infertility, the majority of women are still paying for this service out-of-pocket.[29] Taking this data together, it is important to continue to advocate for more comprehensive fertility preservation coverage across all indications.

Male Fertility Preservation

Sperm cryopreservation is the preferred method for fertility preservation in postpubertal males. While sperm banking is most commonly employed for those with medical conditions or therapies that may compromise spermatogenesis, it is also becoming more frequently utilized for nononcologic indications.[7] Techniques for sperm cryopreservation are well established and typically involve a combination of both slow-cooling and rapid-freezing methods with glycerol as the primary cryoprotectant.[30] Sperms for cryopreservation are most commonly obtained through ejaculation via masturbation, though penile vibratory stimulation or electroejaculation has also been utilized in men with anejaculation.[1,30] In men with obstructive azoospermia or who are unable to produce an ejaculated sample, sperm can be surgically aspirated from the vas deferens, epididymis, or testicle via a percutaneous or open procedure.[31] In male soldiers injured in combat, seminal vesicle aspiration has also been described with encouraging success rates.[8] Testicular tissue cryopreservation is offered at select institutions for prepubertal male patients but is still considered an experimental technique.[32]

Pregnancies using cryopreserved sperm are achieved through the use of ART including intrauterine insemination (IUI), IVF, and ICSI. Pregnancy rates using cryopreserved sperm have increased accordingly with advancements in these technologies, particularly ICSI in which a single live spermatozoa is required for insemination of the oocyte.[1] In a study of 272 men who pursued fertility preservation prior to cancer treatment, live birth rates with IVF–ICSI were reported to be 62.1% which was higher than the males without cancer undergoing the same treatment.[4] These rates are similar to other published reports.[32,33] Similarly, studies comparing the use of fresh and cryopreserved sperm in ART have demonstrated equivalent performance.[34,35] Additionally, cryopreserved sperm can be safely utilized decades later with relatively no impact on clinical success rates.[36] The longest durations of sperm cryopreservation resulting in live births from IUI and IVF are 28 and 40 years, respectively.[37,38] To date, there have been no adverse outcomes reported in offspring conceived through the use of cryopreserved sperm.[32]

The marked benefits of male fertility preservation have been demonstrated to extend beyond the physical ability to achieve parenthood, particularly reflected again in the cancer literature. Male factor infertility has been cited to be one of the most troubling side effects of anticancer treatment.[39] Adolescent and adult cancer patients who choose to bank sperm prior to treatment have demonstrated improved psychological health and postsurvival fatherhood.[40,41] Evidence from UK servicemen who experienced GU injury suggested that men in whom fertility persisted had better injury recovery and quality of life.[42]

Despite the encouraging success rates and multiple benefits to be gained, very few men actually pursue fertility preservation when appropriate. Barriers to fertility preservation include lack of interest, cost of freezing and storage, and most strikingly, not being discussed or offered by their provider.[43] A recent study of male cancer patients found that only 29% of patients received fertility counseling and 11% attempted sperm banking.[44] Though cost is not the most significantly cited obstacle for men who decline fertility preservation, the fees are not negligible. The cost of sperm banking varies across the United States, but most commonly includes a $1,000 initial processing cost with yearly storage fees ranging from $300 to $500.[45] These cost estimates do not factor in the fees associated with ART if needing to utilize their cryopreserved sperm. Similar to oocyte cryopreservation, sperm banking is infrequently covered by insurance, regardless of the indication. In a qualitative analysis by Sonnenburg et al, multiple patients noted that if the cost were covered by insurance, that may have changed their decision to bank.[43] Taken together, these findings stress the importance of timely communication between providers and patients regarding health and occupational hazards that may impact their fertility as well as the benefits associated with sperm cryopreservation.

Gamete Utilization

Reported rates of gamete utilization after fertility preservation in the general population have been variable and are likely underestimated due to the samples that remain in storage.[33,46] Machen et al published a study in 2018 that set to examine the utilization rates and outcomes of cryopreserved sperm in their general male population based on indication for storage. For the 1,442 samples frozen over a 27-year period, total sample utilization rate was 19.3%. Notably, of all cryopreserved samples, 5.5% was cryopreserved prior to military deployment. Military men had a sample utilization rate of 22.8% and the majority of the samples tended to be used within the first year of storage. However, the majority of these men were part of an infertile couple who happened to be deploying during the time of their treatment. Therefore, these utilization rates do not accurately reflect the male population electively freezing sperm prior to deployment. Additionally, this study did not discern whether these men experienced further fertility compromise while in combat which prompted their use of the samples.[47]

A study by Cobo et al in 2016 assessed utilization rates in 1,468 women who pursued fertility preservation for nononcologic indications from 2007 to 2015. In that time interval, 137 women (9.3%) returned to use their frozen eggs with a mean freeze-to-thaw interval of 2.2 years.[3] A study published a year later by Hammarberg et al examined a smaller cohort of women over a longer time period. Of their 193 patients, only

6 returned to use their oocytes (3.1%); however 21% reported intent to use.[48] It would be anticipated that utilization rates may be higher in a population where the probability of GU compromise is increased above that of the general population. Future studies examining the utilization of cryopreserved oocytes in active duty military women will be important to pursue.

Active Duty Military: Reproductive Challenges and Considerations

Active duty military members face multiple obstacles that may impact their future ability to reproduce. The most notable evidence-based risks are the age and marital status at the time of deployment, the risk for gonadal injury in combat, and potential risks of infertility. Women who are found to be pregnant while deployed are required to be evacuated from combat areas. In understanding the ability of pregnancy to impact troop readiness, a woman may elect to delay childbearing beyond her original family planning goals.[49] If a decision to pursue fertility preservation is made, plans for gamete disposition should be thoroughly discussed. Military members should be extensively counseled on their various reproductive risks prior to deployment and have a low threshold for fertility preservation counseling.

Age and Marital Status at the Time of Deployment

There are more than 1 million enlisted members and officers of the active duty military, the majority of which are men and women of reproductive age.[7,49–51] The U.S. DoD data in 2010 showed that average age of military personnel deployed in Operation Iraqi Freedom and Operation Enduring Freedom was 33.4 years with 45% between ages of 25 and 34 years. Sixty percent were married at the time of deployment, but 51% did not have children.[52] Per the most recent military demographic profile in 2017, the average age of active duty enlisted members and officers was 28.3 years. Approximately half of all active duty members were 25 years of age or younger and this age distribution has remained relatively stable over the last decade. Additionally, 42.5% of active duty members reported never being married and 61.6% did not have children. Women currently comprise 16.2% of all active duty personnel.[51] As the number of women joining active duty service continues to increase each year, it is important to provide them with education on age-related fertility decline and the impact that delayed childbearing may have on future reproductive success.[53]

Risk of Combat-Related Genitourinary Injury

Active duty men and women entering combat are at risk for GU injury that may compromise future fertility. A dramatic rise in the rate of GU injury was observed during the U.S. war efforts with Iraq and Afghanistan, primarily due to the heavy use of ground-based explosive devices.[54,55] Soldiers encountering these ground explosives often experienced dismounted complex blast injuries, a characteristic injury pattern involving multi-extremity damage or amputations, pelvic fractures, and genital/perineal injury.[56] With the advancements in emergency combat care, these historically fatal complex blast injuries became survivable, but often leaving the soldiers with significant genital and reproductive morbidities.[54] While the majority of service members experiencing GU injury are men (98.5%), an increasing number of women are entering combat zones and experiencing injuries at similar rates as their male counterparts.[50]

The largest review of military GU injuries was published at the conclusions of Operation Iraqi Freedom and Operation Enduring Freedom in 2017 by Janak et al.[55] Over the 12 years and 30,000 injury codes analyzed through the Department of Defense Trauma Registry (DoDTR), 1,462 (5.3%) service members were reported to have sustained one or more GU injuries. Of these soldiers, 1,000 (73.2%) had one or more injury to the external genitalia and 502 (36.7%) were classified as severe GU injury. To date, there have been no published long-term follow-up studies evaluating future reproductive potential or gonadal function in these service members.

A survey study of UK servicemen who sustained GU injuries in combat reported that experiencing genital injury was more devastating than lower limb amputations. Additionally, their psychological outcomes were improved when their fertility status was known and revealed to them at an early stage.[9] Future directions have been aimed at improving personal protective equipment for both men and women in combat zones which has shown some promise in one observational study.[57] As mentioned previously, options for sperm preservation are available for select injured soldiers; however, there are currently no available means of pursuing female fertility preservation in the setting of combat injury.[8]

Risk for Infertility

The National Health Study for a New Generation of U.S. Veterans, a survey study of veterans who served in Operation Enduring Freedom/Operation Iraqi Freedom, reported a lifetime prevalence of infertility for servicemen and women of 13.8 and 15.8%, respectively. After adjusting for confounding variables, they found similar rates of infertility between men and women; however, they noted that women veterans were more likely to seek care for infertility treatment.[58] Additional studies have demonstrated associations between elevated rates of lifetime sexual assault and infertility or lack of infertility evaluations in female veterans.[59] Given the varied definitions used for surveying the population for prevalence of infertility, direct comparisons between the military and nonmilitary populations are difficult. Reports of various exposures among military personnel and associations with infertility are also conflicting and have multiple limitations.[60,61] At this time, more research is necessary to establish a causal relationship between combat exposures and infertility.

Posthumous Reproduction

Active duty military members and their families who elect to pursue predeployment fertility preservation should consider the disposition of their gametes in the event the soldier dies in combat. Similar to cancer patients undergoing fertility

preservation prior to treatment, an advanced directive for disposition of the gametes should be defined. Posthumous reproduction, or the use of a deceased person's gametes for ART, is permitted by law if the deceased has given explicit directions for them to do so.[62] In a study by Pastuszak et al of 364 men undergoing sperm banking prior to cancer treatment or for the management of infertility, 85.9% consented to posthumous sperm use.[63] As this represents complicated and difficult decision making, proper counseling of soldiers at the time of fertility preservation is critical.

Past, Present, and Future of Fertility Preservation Coverage for Active Duty Military

Historically, there have been no formal policies through the active duty military health care program (TRICARE) that provide coverage for ART or gamete cryopreservation.[7] In 2016, the DoD proposed a pilot program entitled the "*Force of the Future*" which included sperm and oocyte cryopreservation as a covered benefit for active duty military set to deploy. In addition to revising parental leave policies and child care services for military personnel, this program's $38 million request intended to fund initial cryopreservation costs and storage fees for up to 2 years.[7] The goal of the Defense Secretary Ashton Carter was to provide "peace of mind" for deploying troops and "greater flexibility" for family building upon their return, particularly for those who suffered sterilizing combat injuries.[64] Unfortunately, this proposal fell through in Congress in 2017 and there have been no significant attempts to revive it.

Criticisms of the initiative included conservative ideologies and issues with the ART that would be required to use said gametes.[65] The primary controversies that continue to prevent policy change are notably all definable and resolvable issues: storage duration limits, storage fees, and legal ownership of gametes if a soldier dies in combat.[8] Active duty military personnel have the option to pursue predeployment fertility preservation through civilian or military centers at discounted rates, but there is still significant out-of-pocket cost. There are non-for-profit organizations like the Bob Woodruff Foundation that aid in covering costs, but there is little data on how often military personnel choose to utilize these programs for fertility preservation.

There are no published studies evaluating how strongly active duty service members value discussions regarding their reproductive risks, access to fertility services, or the ability to bear biological children as it relates to their deployment. A conference sponsored by the Bob Woodruff Foundation in 2011 titled "*Intimacy after Injury*" offered personal accounts from injured soldiers on the psychological impact of becoming infertile as a result of their service. One spouse of an injured soldier recounted, "When they tell you that you will never have children, you feel completely violated. Why didn't somebody talk to us about banking sperm?"[66] Survey studies in female veterans have demonstrated that they express a strong desire for reproductive life planning.[67] A study evaluating women veterans' reproductive preferences and experiences with VA women's health services concluded that women veterans desired more from their reproductive care and were interested in expanded access to advanced fertility services. One woman was quoted saying, "…I can essentially say that I gave my reproductive years to the Marine Corps. And those are the years you can serve. We serve during our fertile years and we sacrifice…. The VA should probably address that part of womanhood and have that understanding."[68] Further studies in active duty servicemen and women are essential to delineate the attitudes toward advanced reproductive services and whether they would choose to pursue fertility preservation as part of a covered benefit program.

While awaiting future policy change, active duty members of the military should be counseled on the risks, benefits, success rates, cost, and ethical implications of pursuing fertility preservation to make an informed decision prior to deployment. Once a program supporting clinical care is in place, it will require effort by the DoD to ensure soldiers are properly educated on such programming, cryopreservation storage limits and ethical considerations.[42]

Conclusion

Fertility preservation in men and women is safe, successful, and done routinely in the cases of planned gonadotoxic medical treatments. If provided as a covered benefit for active duty soldiers, it is likely that larger numbers would take part in predeployment gamete storage, allowing them to safely secure a portion of their reproductive liberty while risking their lives to protect our country. Senator Patty Murray addressed the Senate with this statement after the "*Force of the Future*" initiative failed to be approved in 2017: "It's hard to imagine any of my colleagues standing up to say that men and women willing to make the ultimate sacrifices for their country – for all of us – should be denied a shot at their dream of a family."[65] Without a federal policy in place, providers caring for servicemen and women must take it upon themselves to provide education on the reproductive risks associated with deployment, the various options for fertility preservation, and financial assistance opportunities available to pursue gamete cryopreservation.

Conflict of Interest
None.

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