Pediatric ovarian tissue cryopreservation: time to lift the experimental label?

As childhood cancer diagnoses increase and treatments improve survivorship, fertility preservation has emerged as an integral component of the comprehensive cancer treatment plan. The 5-year overall survival rate for childhood cancer has increased from 58% in patients diagnosed between 1975 and 1977 to 83% in those diagnosed between 2002 and 2008 (1). The American Society of Clinical Oncology recognizes fertility preservation as a key survivorship issue and utilizes fertility treatment as a quality care measure. Currently, the primary fertility preservation treatment options include embryo cryopreservation, oocyte cryopreservation and ovarian tissue cryopreservation (OTC). For prepubertal girls, OTC is the only option available since their ovaries will not respond to controlled ovarian hyperstimulation necessary for oocyte retrieval. It is also the only option for women who cannot delay starting chemotherapy. While embryo and oocyte cryopreservation are recognized as valid fertility preservation treatments endorsed by organizations such as the American Society for Reproductive Medicine, OTC is still considered experimental. This experimental label, unfortunately, results in limited access and lack of funding, depriving thousands of young girls with cancer of the only fertility preservation treatment that could allow them to be biological mothers in the future.

In this issue of *Fertility and Sterility* the video by Arian et al. (2) further establishes OTC as a viable option for fertility preservation in pediatric female patients diagnosed with cancer prior to undergoing gonadotoxic treatment. They present the case of a 6 year-old female patient diagnosed with aplastic anemia with a planned bone marrow transplantation requiring treatment that will undoubtedly render her infertile. They demonstrate laparoscopic unilateral oophorectomy performed as a piggy-backed procedure for port placement by the pediatric surgeon under general anesthesia. Oophorectomy was followed by ovarian decortication in the operating room and subsequent OTC. The video also reviews various surgical techniques for transplantation of cryopreserved ovarian tissue for future use when the patient is ready to attempt conception (2).

Currently about 100 centers worldwide perform OTC, most under the umbrella of an institutional review board approved protocol. The typical approach utilized today requires removal of ovarian cortical tissue through a laparoscopic approach (unless combined with another open procedure). Laparoscopy to harvest pediatric ovarian tissue can be combined with other medically indicated procedures such as central line placement to minimize risks and inconvenience of a second procedure under anesthesia as well as reduce costs. After cancer treatment, ovarian cortical tissue is thawed and transplanted either orthotopically to remaining ovarian tissue or pelvic peritoneum, or it can be transplanted heterotopically to locations such as the forearm or abdominal wall.

Despite the fact that OTC is the only fertility preservation option for prepubertal girls as well as all females who cannot delay cancer treatment, access in the U.S. is limited, largely due to the experimental label. Many young patients will not receive treatment in close geographic proximity to a center that offers OTC. Even when it is available, OTC is cost prohibitive for many families and insurance companies rarely if ever cover the service. At most centers, patients (or the parents for pediatric patients) at centers offering OTC need to pay fees associated with surgery, cryopreservation and long-term storage. While some foundations and charitable organizations offer financial assistance for fertility preservation treatments such as embryo and oocyte cryopreservation, very few provide aid for OTC due to the experimental label.

Unfortunately, OTC is not a treatment that can quickly demonstrate positive results as defined by live births, which could hasten lifting the experimental label. When evaluating the safety and efficacy of OTC in pediatric patients, the inevitable delay in live births presents a challenge. Younger patients are not ready to become mothers, and there is currently a delay in reports of reimplantation of ovarian tissue harvested from pediatric patients. Additionally, although it is impossible to fully realize the impact of safety and efficacy of OTC due to lack of a registry that would include all OTC cases, recent data does support its use. Since the first live birth as a result of OTC was reported in 2004, as of June 2017 there have been an estimated 130 live births achieved after transplantation of cryopreserved ovarian tissue. This estimate does not include unreported cases and ongoing pregnancies (3). Once thawed cryopreserved ovarian tissue is transplanted, pregnancy rates are encouraging. Van der Ven et al. (4) reported that among 49 women who underwent transplantation of cryopreserved ovarian tissue with a follow-up >1 year, pregnancy and delivery rates were 33 and 25%, respectively. Similarly, Meirow et al. (5) reported on 20 patients who underwent transplantation of cryopreserved ovarian tissue with 16 total pregnancies; 53% of patients conceived and 32% delivered at least once.

From a patient care perspective, access to OTC in the U.S. will be limited until the experiment label is lifted. Only then will insurance companies fully consider coverage of the harvesting procedure and more foundations will provide financial assistance to patients who would potentially benefit. As the video by Arian et al. (2) demonstrates, for pediatric patients and those who cannot delay treatment, ovarian tissue cryopreservation is not only the only option, but it can be safely performed in young patients who will reap great benefits in the future. As successful live births as a result of OTC continue to be reported, hopefully the experimental label will be lifted. Removing this label would allow greater access to OTC and avoid the devastating effects of gonadotoxic treatment in this vulnerable young age group.

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https://doi.org/10.1016/j.fertnstert.2018.03.035

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