Experimental methods to preserve male fertility and treat male factor infertility

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Infertility is a prevalent condition that has insidious impacts on the infertile individuals, their families, and society, which extend far beyond the inability to have a biological child. Lifestyle changes, fertility treatments, and assisted reproductive technology (ART) are available to help many infertile couples achieve their reproductive goals. All of these technologies require that the infertile individual is able to produce at least a small number of functional gametes (eggs or sperm). It is not possible for a person who does not produce gametes to have a biological child. This review focuses on the infertile man and describes several stem cell-based methods and gene therapy approaches that are in the research pipeline and may lead to new fertility treatment options for men with azoospermia. (Fertil Steril® 2016;105:256–66. ©2016 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

Key Words: Fertility, infertility, azoospermia, stem cells, transplantation, grafting, culture, de novo testicular morphogenesis, gene therapy

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In vitro fertilization was pioneered in the United Kingdom by Drs. Patrick Steptoe (physician) and Robert Edwards (researcher) (1) and led to the birth of Louise Brown (born July 25, 1978), the world's first baby conceived in a Petri dish. This technology has now led to the birth of nearly five million babies worldwide and the 2010 Nobel Prize in Medicine for Dr. Edwards. Despite this progress in treating infertile couples, many still remain beyond the reach of current assisted reproductive technology (ART) because they are not able to produce mature sperm or eggs. For those couples, there are several methods in the research pipeline that may expand fertility options and lead to the next renaissance in the field of assisted reproduction. This review focuses on experimental options to preserve male fertility and/or treat male factor infertility.

Spermatogenesis is an extraordinarily productive process that yields millions of sperm each day throughout the postpubertal life of men (2). Spermatogenesis arises from a relatively small pool of spermatogonial stem cells (SSCs) that are located in the seminiferous tubules of the testis (3–5). These adult tissue stem cells (designated Adark and Apale spermatogonia in humans) balance self-renewing divisions that maintain the stem cell pool with differentiating divisions that insure continuous sperm production (Fig. 1) (6–8). Therefore, SSCs are essential for spermatogenesis and male fertility. Conditions that compromise the stem cell pool, the differentiation process, or the testicular environment (e.g., genetic, environmental, medical, age, injury) can lead to subfertility or infertility. Refinements in ART, including testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI), now allow many men with azoospermia (no sperm in their ejaculate) to father biological children from rare sperm that are biopsied directly from the testes (Fig. 2A) (10–12). At present, there are no options for men with azoospermia and failed TESE to have biological children.

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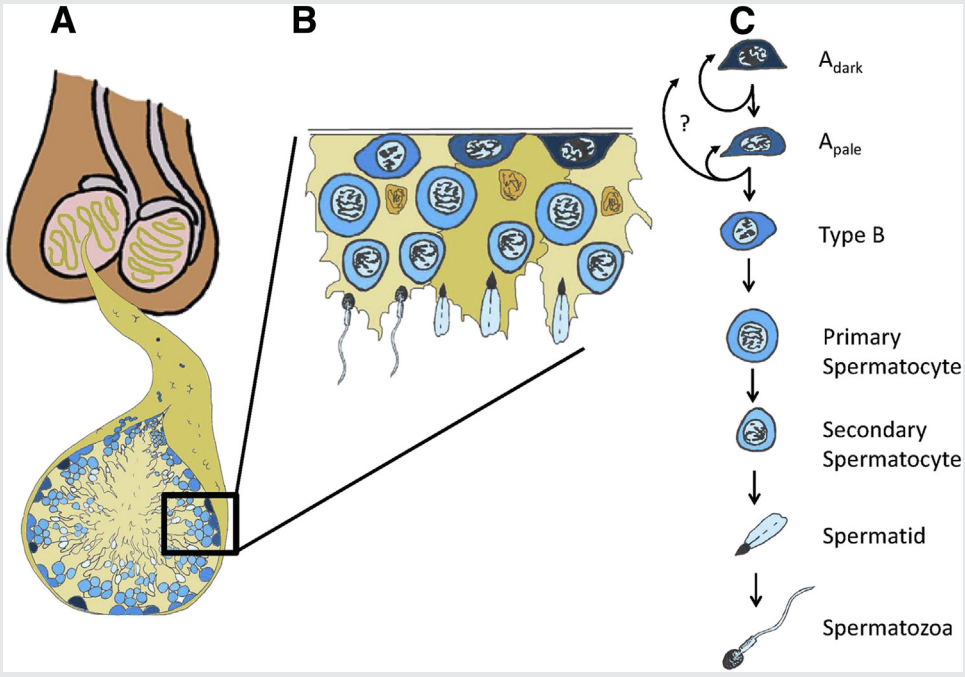
FIGURE 1



Human spermatogonial stem cells and spermatogenesis. (**A**) Spermatogenesis occurs inside the seminiferous tubules of the testis. (**B**) Cut-out of the basement membrane of the seminiferous tubule. (**B** and **C**) The basement membrane of the seminiferous epithelium contains undifferentiated (Adark and Apale) spermatogonia and differentiating type B spermatogonia. Type B spermatogonia give rise to primary spermatocytes that enter meiosis and migrate off the basement membrane. Subsequent meiotic divisions and spermiogenesis give rise to secondary spermatocytes, spermatids, and the terminally differentiated spermatozoa, which are released into the lumen of the seminiferous tubules. (Figure reprinted from Valli et al.[9] with permission from Elsevier. Artwork is by Dr. Bart Phillips, National Institute of Environmental Health Sciences.)

Gassei. Experimental therapies for male factor infertility. Fertil Steril 2016.

Several technologies have emerged during the past two decades that may substantially increase the number of reproductive options available to men who do not produce any sperm and desire to have biological children: SSC transplantation; SSC culture; testicular tissue grafting; testicular tissue organ culture; induced pluripotent stem cells; the $1,000 genome; and gene therapy (Fig. 2). This review describes two patient scenarios to illustrate how these technologies could be used to preserve fertility and generate or regenerate spermatogenesis in men with azoospermia. The first scenario is the prepubertal cancer patient who cannot preserve a semen sample before initiation of treatment and who grows up to become an infertile adult survivor of childhood cancer. The second scenario is a man with idiopathic nonobstructive azoospermia and no previous comobidities.

PATIENT SCENARIO 1: MEDICALLY INDUCED (IATROGENIC) AZOOSPERMIA

Chemotherapy and radiation treatments for cancer and other conditions can cause permanent infertility. Adult men have the option to cryopreserve a semen sample before the initiation of treatment and use this sample in the future to achieve a pregnancy with their partner using ART (Fig. 2A) (1, 13, 14). This option is not available to prepubertal boys who are not making sperm or to adult survivors who did not preserve sperm before treatment. This is a significant human health problem because we estimate that each year in the United States there are >4,000 male patients who will receive treatments that put them at risk of permanent azoospermia and did not or could not save a semen sample (Valli et al. [8, 9]). Testicular sperm extraction may be an option for azoospermic adult survivors of childhood cancers who did not save semen or testicular tissue. This is possible because a few SSCs may survive the gonadotoxic therapy and produce focal areas of spermatogenesis in the seminiferous tubules, which can be retrieved by biopsy. Picton and colleagues (20) surveyed results from five centers and reported an overall sperm recovery rate of 44% in patients with azoospermia undergoing TESE after chemotherapy (15–20). Prepubertal boys cannot save a semen sample before therapy, but they do have Adark and Apale SSCs in their testes (Fig. 1) (21) that are poised to initiate sperm production during puberty. Several centers in the United States and around the world are collecting (through biopsy) and cryopreserving testicular tissue or cells with anticipation that experimental SSC-based therapies will be available in the future (experimental options are reviewed later and in Fig. 2) (20, 22–27).