Asian Journal of Andrology (2016) 18, 364

www.asiaandro.com; www.ajandrology.com

Open Access

INVITED COMMENTARY

Male Fertility

Stem cells, gene therapy, and advanced medical management hold promise in the treatment of male infertility

Ryan P Smith[1], Larry I Lipshultz[2], Jason R Kovac[3]

Asian Journal of Andrology (2016) **18**, 364; doi: 10.4103/1008-682X.179249; published online: 8 April 2016

Medical management of male infertility has traditionally involved therapies directed toward manipulation of the hypothalamic-pituitary-gonadal axis. The medications available currently are essentially identical to those utilized decades ago. Moreover, these agents require that the infertile patient can produce at least a small number of functional sperm. As conveyed by Dr. Ring *et al.*[1] in the accompanying manuscript, a significant percentage of male infertility is defined as "idiopathic" suggesting a specific diagnosis was impossible. Moreover, given that a subset of these patients is postulated to have unrecognized genetic etiologies, the notion of targeted medical treatment becomes even more problematic. Many patients are thus placed on empiric therapy in hopes of augmenting baseline spermatogenic function. While this may prove fruitful in patients with intact spermatogenesis, the true challenge lies in the treatment of the azoospermic patient due to testicular failure.

Technologies have emerged in the last decades that hold promise. Given the limitations reported with the currently available empiric medical therapy, there is a clear need for research advances. Some areas that seem poised for such growth include stem cell biology and gene therapy. Indeed, the potential for stem cells to restore fertility following chemotherapy/radiation in men with cancer has been gaining momentum. Brinster and colleagues, in 1994, reported on successful transplantation of mouse spermatogonial stem cells into the seminiferous tubules of infertile recipient mice.[2] This research led to donor-derived spermatogenesis and subsequent paternity.[2] Since then, others have focused on development, proliferation, and differentiation of mature sperm *in vitro*. The human application requires cryopreservation of tissues before gonadotoxic therapies or, alternatively, harvesting of stem cells from other somatic tissues. Given that there have been reports of *in vitro* propagation of human prepubertal somatic stem cells, these goals do not seem impossible to obtain.[3] Coupled with the fact that testicular tissue is being obtained and cryopreserved under experimental protocols from prepubertal patients preparing to undergo gonadotoxic therapy, the potential use of this type of therapeutic modality may soon become reality.

Given that many men present with as yet-to-be-identified genetic defects, the notion of gene therapy holds high hopes. Such a treatment would theoretically be able to deliver absent/altered downstream genetic products to complete the cycle of spermatogenesis. A simple example of successful genetic manipulation can be seen in the use of viral vectors to create transgenic animals,[4] thus proving the technology exists. Obviously, caution is warranted since genetic perturbations in humans could result in unintended consequences for both offspring and the patient themselves.

Perhaps an untapped resource in the medical management of male infertility lies in the use of growth hormone (GH). GH receptors have been identified throughout the male reproductive tract and IGF-1 receptors are found in secondary spermatocytes and spermatids.[5] There is currently a paucity of research on the effects of GH supplementation in infertile patients. While GH may have an important physiologic role in spermatogenesis, more studies are needed to define the role of GH therapy in clinical practice.

REFERENCES

1 Ring JD, Lwin AA, Köhler TS. Recent advancements in the study of male reproduction current medical management of male infertility. *Asian J Androl* 2016; 18: 357–63. [Doi: 10.4103/1008-682X.179252] [Epub ahead of print].
2 Brinster RL, Zimmermann JW. Spermatogenesis following male germ-cell transplantation. *Proc Nat Acad Sci U S A* 1994; 91: 11298–302.
3 Long CJ, Ginsberg JP, Kolon TF. Fertility preservation in children and adolescents with cancer. *Urology* 2016. [Doi: 10.1016/j.urology.2015.10.047] [Epub ahead of print].
4 Gassei K, Orwig KE. Experimental methods to preserve male fertility and treat male factor infertility. *Fertil Steril* 2016; 105: 256–66.
5 Harvey S, Baudet ML, Murphy A, Luna M, Hull KL, *et al*. Testicular growth hormone (GH): GH expression in spermatogonia and primary spermatocytes. *Gen Comp Endocrinol* 2004; 139: 158–67.

[1]University of Virginia, Department of Urology, Charlottesville, VA 22908, USA; [2]Scott Department of Urology, Baylor College of Medicine, Houston, Texas 77030, USA; [3]Men's Health Center, 8240 Naab Road, Suite 220, Indianapolis, Indiana 46260, USA.
Correspondence: Dr. JR Kovac (jkovac@urologyin.com)