
Editorial Commentary

Hussein A, Ozgok Y, Ross L, Niederberger C. Clomiphene administration for cases of nonobstructive azoospermia: a multicenter study. *J Androl.* 2005;26:787–791.

Azoospermia is present in ~10%–15% of men evaluated for infertility, with nearly two thirds of these men having nonobstructive azoospermia (NOA; Ghanem et al, 2005). Until recently, men with NOA were forced to rely on donor sperm for conception. However, the introduction of intracytoplasmic sperm injection (ICSI) has allowed the use of extremely small numbers of sperm to be used for fertilization, even in the absence of progressive motility. Moreover, with the advent of testicular sperm retrieval, even men with spermatogenic failure have been demonstrated to have limited sperm production, thus allowing them the chance for biological fatherhood (Devroey et al, 1995). However, in the absence of potentially reversible conditions, such as varicoceles, men with NOA almost universally require surgical sperm retrieval for use with in vitro fertilization.

Methods for retrieval of these small numbers of sperm vary, from open testicular biopsy to percutaneous needle aspiration (Friedler et al, 1997). Most centers have demonstrated fairly consistent pregnancy rates with surgically retrieved testicular sperm, although some centers report that men with obstructive azoospermia tend to have better outcomes than those with NOA (Mansour et al, 1997). Furthermore, men with NOA typically require sperm retrieval in cycle with egg retrieval, thus exposing both partners to surgical procedures on the same day. Finally, there have been some reports of increased delivery rates with ejaculated sperm compared with surgically retrieved sperm from men with NOA, although these groups are not directly comparable for obvious reasons (Ubaldi et al, 1999).

Clomiphene citrate is an antiestrogen that has been used for several decades in the treatment of idiopathic infertility in men (Mellinger and Thompson, 1966). The rationale for its use in these men is that by inhibiting the negative feedback of endogenous estrogens, the hypothalamus will secrete increased levels of GnRH, thus leading to an increase in luteinizing hormone and follicle-stimulating hormone secretion and, ultimately, in testosterone and sperm production. Multiple studies have examined the efficacy of clomiphene treatment in men, with

conflicting results (Ronnberg, 1980; World Health Organization, 1992). Some studies have shown an improvement in seminal parameters, either with or without a concomitant increase in natural conception. Other studies have demonstrated no beneficial effect on either of these parameters. Thus, the use of clomiphene, although somewhat controversial, is not uncommon.

This report demonstrates that in select men, clomiphene citrate usage was able to restore viable sperm to the ejaculate in nearly two thirds of men with biopsy-proven spermatogenic arrest. This represents a significant step for these patients, thus allowing them to use ejaculated sperm without having to undergo surgical sperm retrieval. The authors titrated the dosage to produce a testosterone level of 600–800 mg/dL, which represented levels well within the normal range for serum testosterone. The rationale was that clomiphene would increase endogenous gonadotropin secretion, thus leading to increased intratesticular testosterone and potentially improved spermatogenesis. This is supported by the nearly two thirds of men who had a return of viable sperm to their ejaculate. Furthermore, in those men who remained azoospermic, all had successful testicular sperm retrieval, with the pattern of spermatogenesis in their posttreatment biopsy demonstrating improved spermatogenesis.

One of the strengths of the paper is that all patients had multiple semen analyses demonstrating azoospermia before clomiphene treatment. Because it is well established that men with NOA can occasionally show sperm in their ejaculate, the consistent azoospermia of these men makes the posttreatment data more significant. Another strength is that all patients had preoperative biopsies demonstrating either late maturation arrest or hypospermatogenesis. Although a potential criticism is that a random biopsy is not necessarily reflective of the entire testis, the biopsy data, in combination with the azoospermic semen analyses, strengthens the study. Finally, posttreatment biopsies demonstrating improved spermatogenesis in the patients who remained azoospermic allows the authors to demonstrate potential benefit, even in those men who did not experience return of sperm to their ejaculate. However, it should be pointed out that this population of men with late maturation arrest, hypospermatogenesis, or both

tend to have fairly high rates of successful testicular sperm retrieval.

However, this study has several flaws that deserve mention. First, this is not randomized, nor is it controlled; therefore, the study is open to bias. It is well known that even azoospermia is not absolute and there is variability in the appearance of sperm in the ejaculate of men with testicular failure (Tournaye et al, 1995). Furthermore, with the diagnosis made based on a single random biopsy, it is very possible that some of these men were placed into the wrong category. One needs to be careful about drawing conclusions regarding improvement in posttreatment biopsies on the basis of single, random samples. Finally, this is a small group of patients; therefore, the study lacks statistical power.

However, despite these flaws, this interesting study brings up some salient points. What is the role of clomiphene in male infertility? Would men who fail to respond to clomiphene potentially respond to gonadotropins? I think the authors are to be congratulated for presenting some interesting data that might help select couples conceive without the need of an invasive procedure.

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