On-label and off-label drugs used in the treatment of male infertility

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Infertility affects 6.1 million U.S. couples—representing 10% of reproductive-age adults and 15% of all couples trying to conceive. Half of the time, infertility is the result of an abnormal semen analysis or other male factors, with 40%–50% of these infertile men diagnosed with idiopathic or nonclassifiable infertility. While the role of hormone therapy for men with an identified abnormality is well defined, the literature remains inconclusive and controversial regarding hormone manipulation using empirical (off-label) medical therapies for men with idiopathic infertility. This manuscript reviews the commonly used off-label medications used to treat idiopathic male factor infertility: clomiphene citrate, letrozole/anastrozole, exogenous androgens, and pentoxifylline. (Fertil Steril® 2015;103:595–604. ©2015 by American Society for Reproductive Medicine.)

Key Words: Infertile men, idiopathic, off-label, empirical

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Infertility affects 6.1 million U.S. couples—representing 10% of reproductive aged adults (1) and 15% of all couples trying to conceive (2). Moreover, there has been a steady increase in the number of couples seeking consultation for infertility over the past decade (3). Half of the time, infertility is the result of an abnormal semen analysis or other male factors (4), with 40%–50% of these infertile men diagnosed with idiopathic or nonclassifiable infertility (5). While the role of hormone therapy for men with an identified abnormality is well defined (6), the literature remains inconclusive and controversial regarding hormone manipulation using empirical (off-label) medical therapies (EMT) for men with idiopathic infertility (7).

In the absence of a clearly correctable medical or surgical condition, men with idiopathic infertility are left with the option of assisted reproduction and/or an attempt to improve their reproductive potential using EMT (8). Use of empirical therapy for infertile men is confounded by the lack of both Food and Drug Administration (FDA) approval and use recommendations/guidelines by any professional medical organization (7). Nonetheless, use of EMTs in this patient population is widespread. A recent survey by Ko et al. reported that two-thirds of responding U.S. urologists would use EMT to treat idiopathic male factor infertility. They reported that the most commonly used medications were clomiphene citrate, hCG, and anastrozole, with survey respondents using EMT for 3–6 months (61%), 12 months (24%), and over 12 months (0.9%) and the remainder treating for less than 3 months (7). Interestingly, 25% of respondents reported using exogenous T to treat such men (7). Trying to figure out whom to treat with EMTs can be challenging. For instance, exogenous T is not effective for promoting fertility and has, on the contrary, been used as a male contraceptive.

Effectiveness of empirical treatment on male factor infertility has been evaluated by many groups, including Cochrane meta-analyses, with inconclusive results. On the one hand, studies have demonstrated that EMT use in infertile men can increase both pregnancy rates (9–11) and sperm counts (11–13). On the other hand, competing studies were unable to conclusively confirm such outcomes (14–16). A Cochrane meta-analysis from 2000 reviewed 10 randomized controlled trials investigating clomiphene or tamoxifen use for idiopathic oligo-/asthenospermia (17). Although the treated men demonstrated improved endocrine/hormone parameters, improved pregnancy rates were not realized. Studies included in this review varied in their treatment schedules, use of placebo arms, and randomization schemes—limiting this review's conclusions (17). A more recent Cochrane meta-analysis reviewed pregnancy rates after gonadotropin use in males with idiopathic infertility (18). Pooled data from four randomized, controlled trials

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demonstrated a pregnancy rate of 13.4% versus 4.4% for those without treatment (odd ratio [OR], 3.03; 95% confidence interval [CI], 1.30 to 7.09). Study power was limited by inadequate enrollment numbers, limiting the conclusions from this meta-analysis (18).

FDA APPROVED: GONADOTROPINS

Gonadotropins are the only class of medications approved by the FDA for the medical management of male factor infertility. Gonadotropins include GnRH, LH, and FSH and are used to treat hypogonadism and hypospermatogenesis (Table 1). Hypogonadism refers to a decrease in function of Sertoli and/or Leydig cells—resulting in a decrease in sperm and/or T production. The cause of hypogonadism may arise from either testicular hypofunction (primary failure) or lack of hypothalamus-pituitary axis stimulation (secondary failure), also called hypogonadotrophic hypogonadism (HH). With secondary hypogonadism, both LH and FSH levels are reduced, resulting in low T and suboptimal spermatogenesis (19). Current on-label treatment options include direct stimulation of the anterior pituitary (using pulsatile GnRH) or exogenous replacement of LH/FSH (gonadotropins).

Pulsed GnRH therapy uses a pump to administer 25 to 600 ng/kg every 2 hours with an adequate response often taking 1–3 years (20). Success with GnRH replacement is more likely in a post-pubertal male without a history of cryptorchidism, and, with an inhibin B level of over 60 pg/ml (21). Of note, pulsed GnRH therapy is not available in the United States.

Development of HH before or after puberty defines the initial gonadotropic replacement regimen. If HH occurs after puberty, Sertoli cells have already been primed by FSH and gonadotropin replacement may require only hCG, an LH analog (22). On the other hand, prepubertal HH will require both FSH and LH replacement—at least initially (23). After priming with both FSH and LH, ongoing spermatogenesis and T production usually only requires LH/hCG replacement. If the timing of HH onset is unclear, a testicular volume of less than 4 mL may help to identify that patient as most likely having prepubertal HH (23).

HCG has the biological activity of LH and exists in both a recombinant form, and as a urinary extract. Recombinant LH is available, but its shorter half-life (of 10 hours) limits utility. hCG can be given intramuscularly or subcutaneously three-times per week starting with an initial dose of 1000 units. If the targeted testosterone level is not obtained after two months, consider increasing the hCG dose by 50 percent. Moreover, if adequate spermatogenesis (>15 M/mL) is not achieved by 18 months of hCG exposure, consider adding an FSH product (24). There are several reasons to try hCG replacement alone before adding an FSH product: [1] hCG is more cost effective, [2] hCG will increase intratesticular T concentrations (up to 100 times that of peripheral blood), and [3] hCG alone may be all that is needed to prompt spermatogenesis.

Like hCG, FSH products are available in different formulations. FSH was first extracted from urine (25–27), followed by recombinant FSH, and more recently, recombinant-human FSH (r-h FSH) (28–30). For FSH replacement, consider starting with 150 IU rh-FSH every other day for the first 6 months; then increase the dose by 75 IU if no sperm is present, followed by a second dose escalation of an additional 75 IU/dose at 12 months (24). Recovery of spermatogenesis may be further enhanced by adding clomiphene citrate (see off-label section) before FSH administration (31).

HMG contains purified extracts of both FSH and LH. Again, the FSH component may be needed to initiate spermatogenesis in a male with prepubertal HH. Consider starting with 75 units (one vial) of hMG 3 times a week, increasing the hMG dose to 150 units (two vials) if sperm concentration is not adequate (>15 M/mL) by 6 months. Once sperm is present, consider discontinuing the expensive hMG while continuing hCG to maintain spermatogenesis.

A Cochrane review of six randomized controlled trials suggested a beneficial effect on live birth and pregnancy rates when men with idiopathic male subfertility were treated with gonadotropins. From 456 participants (with varied treatment and follow-up schedules), it was determined that the live-birth rate was 27% versus 0% (OR, 9.31; 95% CI, 1.17–73.75) and the spontaneous pregnancy rate per couple was 16% versus 7% (OR, 4.94; 95% CI, 2.13–11.44) when comparing those treated with gonadotropins with those receiving a placebo or the no-treatment arm (18).

OFF-LABEL USE (TABLE 2)

Clomiphene Citrate (CC)

CC is a nonsteroidal estrogen agonist/antagonist existing as a racemic mixture of two isoforms (En-clomiphene and Zu-clomiphene) (32). This selective estrogen receptor modulator blocks the negative feedback of estrogen at the pituitary/hypothalamus level, thereby indirectly enhancing LH and FSH excretion from the anterior pituitary. Increased LH/FSH stimulation of the testes should increase both T production and spermatogenesis, respectively. Studies have demonstrated that CC has resulted in moderate elevations in both LH/FSH and sperm concentration in patients with pregerminal hypofertility (10, 33) and in those with unexplained infertility (34, 35). More recently, exclusive use of the en-clomiphene isoform (instead of the racemic mixture) demonstrated increased morning T levels and spermatogenesis preservation (36).

In contrast, there are negative studies reporting that CC results are no better than those of placebo (37) or in untreated controls (38)—especially when looking at pregnancy outcomes (15).

Optimal CC dosing in males has not been established (32, 33, 39). Recommended doses range from 12.5 to 400 mg/day, with one study reporting that 100 mg 3 times a week was safe for up to 15 months (35). Studies have included the following dosing schedule: daily, alternate day, and cyclical (25 days medicated, followed by 5 days of "rest"). Current dosing schedules tend to start with a low dose (25 mg daily or 50 mg every other day) and, if needed, an increase to 50 mg daily to optimize outcome.

CC's effect on outcome measures such as improvement in T levels or semen analysis is not immediate. Regarding sperm parameters, the first improvement tends to be percent motility