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 (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, 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 (EMTs) 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...
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 gonadotrophic 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 times a week, increasing the hMG dose to 150 units (two vials) if 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 Zuclotheme) [32]. This selective estrogen receptor modulator blocks the negative feedback of estrogen at the pituitary/hypothalamic 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...
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<th>Drug</th>
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<tr>
<td>GnRH</td>
<td>When pulsatile, stimulates LH release from anterior pituitary</td>
<td>Renal, urine; 10–40 min</td>
<td>Induction of ovulation in females with hypothalamic amenorrhea</td>
<td>Injection site irritation, superficial thrombophlebitis</td>
<td>None established</td>
<td>None established: X</td>
<td>Women with any condition (pituitary prolactinoma) that could be exacerbated by pregnancy; patients who have ovarian cysts; any condition (hormone-dependent tumor) that may be worsened by reproductive hormones</td>
</tr>
<tr>
<td>hCG (LH-like); Novarel Pregnyl</td>
<td>Stimulates Leydig cells (T)</td>
<td>Urine; not reported</td>
<td>Prepubertal cryptorchidism, hypogonadism, and ovulation induction</td>
<td>Arterial thromboembolism, acne, testis pain, gynecomastia, allergy symptoms, injection site pain</td>
<td>None established</td>
<td>None established: C</td>
<td>Precocious puberty, prostatic carcinoma or other androgen-dependent neoplasia, and pregnancy</td>
</tr>
<tr>
<td>hMG (LH- and FSH-like); Menopur Repronex</td>
<td>Stimulates Leydig and Sertoli cells (T and spermatogenesis)</td>
<td>Urine; 11–60 h</td>
<td>For multiple follicle development and pregnancy in ovulatory women</td>
<td>Headache, nausea, abdominal pain, injection site pain</td>
<td>None established</td>
<td>Ectopic pregnancy, congenital abnormalities, spontaneous abortion, and multifetal gestations/births: X</td>
<td>Primary ovarian failure (with high FSH); uncontrolled nongonadal endocrinopathies (thyroid, adrenal, pituitary); pituitary or hypothalamic tumors; abnormal uterine bleeding of undetermined origin; ovarian cyst or enlargement not due to polycystic ovary syndrome; pregnancy</td>
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<tr>
<td>FSH: Recombinant FSH (r-FSH); Gonal Follicin</td>
<td>Stimulates Sertoli cells (spermatogenesis)</td>
<td>Not reported; 32–41 h</td>
<td>Ovulation and spermatogenesis induction</td>
<td>Acne, fatigue, flu symptoms, upper respiratory symptoms, seborrhea, gynecomastia, sinusitis, varicocele</td>
<td>None established</td>
<td>Ectopic pregnancy, congenital abnormalities, spontaneous abortion, and multiple births have been reported. The incidence of congenital abnormality may be slightly higher after ART than with spontaneous conception: X.</td>
<td>High levels of FSH indicating primary gonadal failure (ovarian or testicular); sex hormone-dependent tumors of the reproductive tract and accessory organs; intracranial lesions (pituitary or hypothalamus tumor); uncontrolled thyroid, pituitary or adrenal dysfunction</td>
</tr>
<tr>
<td>CC; clomid</td>
<td>Nonsteroidal estrogen agonist/antagonist. Disrupts negative feedback of estrogen on the hypothalamus and pituitary</td>
<td>Feces via biliary tract; 5 d</td>
<td>Female factor infertility, ovulation induction</td>
<td>Headache, nausea, visual disturbances, dizziness, abdominal discomfort, mouth ulcers, cataract formation</td>
<td>None known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI; feomara; letrozole; anastrozole</td>
<td>Down-regulate production of estrogen by reversibly inhibiting cytochrome P450 isoenzymes (2A6 and 2C19) of the aromatase enzyme complex</td>
<td>Renal; 2 d</td>
<td>Breast cancer, female infertility</td>
<td>Loss of libido, cutaneous rash, osteoporosis, hypercholesterolemia, fatigue, dizziness, drowsiness</td>
<td>Tamoxifen: coadministration reduces letrozole plasma levels by 38%</td>
<td>Human teratogen; X</td>
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<td>Androgens; mesterolone, T, undeconoate</td>
<td>Responsible for promoting the growth and development of the male sex organs and maintaining secondary sex characteristics in androgen-deficient males.</td>
<td>Hepatic, urine; variable 10–100 min</td>
<td>Andro-pause, delayed male puberty</td>
<td>Erythrocytosis/clots, acne, prostate cancer progression, decreased fertility</td>
<td>None known</td>
<td>Masculinization of the female fetus; X</td>
<td>Pregnant females, breast/prostate cancer, erythrocytosis (HCT &gt; 52%–54%), obstructive sleep apnea, heart failure, severe BPH, desire for fertility</td>
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<td>PF; trental</td>
<td>Methylxanthine derivative, competitive nonselective phosphodiesterase inhibitor. Increases blood flow to the affected microcirculation. Blood viscosity is lowered, erythrocyte flexibility is increased, leukocyte deformability is increased, and neutrophil adhesion and activation are decreased.</td>
<td>Hepatic, urine; drug: 24–48 min; metabolites: 60–96 min</td>
<td>Intermittent claudication</td>
<td>Gastrointestinal: nausea, vomiting, indigestion</td>
<td>Increases anticoagulation effect of heparin, nonsteroidal anti-inflammatory drugs. Ketolarac enhances anticoagulation effect. Enhances hypotensive effect of antihypertensives. Increases effect of theophylline</td>
<td>C</td>
<td>Xanthine intolerance (caffeine, theophylline), recent cerebral/retinal hemorrhage</td>
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Note: C (pregnancy category): Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; C X (pregnancy category): Studies in animals or humans have demonstrated fetal abnormalities.

## TABLE 2

Off-label medications used for idiopathic male factor infertility.

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When defining an adequate CC response as a pregnancy or a 100% improvement in total motile sperm count, Ross et al. found that more than 50% of patients (35 of 53 subjects) responded by 3 months, with the remainder taking 6–15 months to respond. Many were “late responders”; if pregnancy does not occur, consider treating with CC for 12–15 months [39].

Detrimental effects of CC on sperm parameters have been reported. Ross et al. reported that one of 53 patients on high-dose clomid (100 mg 3 times/week) suffered a decline in total motile sperm count, which rapidly improved when the dose was reduced to 50 mg every other day [39]. Moreover, there is a case report of three men becoming azoospermic after CC use, with return to severe oligospermia after discontinuation (CC dose or schedule was not reported) [40].

AIDs are nonsteroidal inhibitors that cause reversible enzyme inhibition. Although anastrozole or letrozole suppress the production and release of FSH (46). AIs down-regulate the production of estrogen by reversibly inhibiting the cytochrome P450 isozymes 2A6 and 2C19 of the aromatase enzyme complex. This inhibits the negative feedback loop of estrogen on the hypothalamus, resulting in stronger GnRH pulses. The elevated GnRH pulses stimulate the pituitary to produce more FSH, stimulating Sertoli cells and positively impacting spermatogenesis (47). Thus, AIs have the ability to increase the levels of endogenous T without the associated increase in estrogen levels seen with CC [48].

Pavlovich et al. identified a specific endocrine defect in men with severe male factor infertility that causes impairment of sperm production due to a relative excess of estrogen to T (47). This is quantitatively measured as the T:E ratio. A low T:E ratio has been associated with defective spermatogenesis [48], with some clinicians suggesting treatment for a T:E ratio less than 10:1 [49]. EMT with AIs may potentially reverse the low T:E ratio, with the increased T levels improving spermatogenesis. After treatment, an increase in T:E ratio has occurred with associated increases in semen parameters (45, 50). Current off-label doses include 1 mg of anastrozole (50) and 2.5–5 mg of letrozole given daily (51, 52).

Treatment of infertile men with low serum T levels using AIs is rational and has been associated with [1] improved sperm concentration from 5.5 to 15.6 million sperm/mL (45), [2] increased serum T from 14 to 28 nmol/L (45), and [3] suppressed E2 levels (45). Currently, there are no prospectively randomized controlled trials, and the use of AIs remains off label. Further studies are needed to better evaluate the effects of AIs on spermatogenesis and to evaluate pregnancy rates post-treatment.

**Anastrozole and Letrozole**

Anastrozole and letrozole are prescription medications that belong to the class of aromatase inhibitors (AIs). AIs are classified as either steroidal or nonsteroidal. Steroidal inhibitors (such as testolactone, forimestane, and exemestanes) competitively inhibit aromatase by mimicking androstenedione—causing irreversible enzyme inhibition. Letrozole and anastrozole are nonsteroidal inhibitors that cause reversible enzyme inhibition. Although anastrozole or letrozole suppression is close to 100% in women, men do not show such a profound decrease—likely related to their high plasma T levels (43, 44). Nonetheless, letrozole is a more potent AI than anastrozol (45), with both being used off label for treating oligospermia and azoospermia (44).

In men, the majority of estrogen is made by the aromatize enzyme complex, which converts T into E2 and androstenedione to estrone. E2 plays an important role in the negative feedback on the hypothalamus–pituitary axis to down-regulate the production and release of FSH (46). AIs down-regulate the production of estrogen by reversibly inhibiting the cytochrome P450 isozymes 2A6 and 2C19 of the aromatase enzyme complex. This inhibits the negative feedback loop of estrogen on the hypothalamus, resulting in stronger GnRH pulses. The elevated GnRH pulses stimulate the pituitary to produce more FSH, stimulating Sertoli cells and positively impacting spermatogenesis (47). Thus, AIs have the ability to increase the levels of endogenous T without the associated increase in estrogen levels seen with CC (48).

Androgens are essential for the development of male reproductive organs (penis, prostate, seminal vesicles, vas deferens, and epididymis) and for subsequent puberty, sexual function, and fertility. Androgen receptors (ARs) are found in all male reproductive organs and are stimulated by T and its more potent derivative, dihydrotestosterone (DHT) (53). High levels of intratesticular T are necessary for spermatogenesis, in part because the testes lack 5α-reductase and therefore lack exposure to the more potent DHT. One job of intratesticular T is to promote AR expression (54), which is required for spermatogenesis. Infertile men frequently (26 of 1,517 men: 1.7%) have AR gene mutations. Unfortunately, the ability to determine who should be screened for AR mutations does not exist (55). Since ARs do not discern between endogenous (Leydig-based) and exogenously administered T, some (up to 25%) urologists (7) have used T replacement therapies in an attempt to improve fertility. Unfortunately this does not work, as the exogenous T ultimately inhibits pituitary LH/FSH production. In fact, exogenous T is used to promote infertility as a form of male birth control (56). Moreover, the 2013 European Association of Urology Guidelines on Male Infertility clearly state that “T suppresses pituitary production of LH and FSH, therefore, replacement therapy should not be given for infertility” (57).

Samplaski et al. looked at exogenous T use in a cohort of 4,400 men attending an infertility clinic; 59 men (1.3%) reported taking T—82% to treat hypogonadism and 12% (seven of 59) to treat infertility. While on T, 88% were azoospermic, with 65% recovering spermatogenesis 6 months after discontinuing T (if no other reason for azoospermia existed) (58). Another study used a meta-analysis to report that 94% of men stopping exogenous T—prescribed for male birth control—recovered spermatogenesis (>20 million sperm/mL) (59). Unfortunately, not all men will recover spermatogenesis after exogenous T use. Notably, spermatogenesis recovery is...
more likely with [1] use of shorter acting T preparations, [2] higher baseline sperm concentration, [3] faster suppression of spermatogenesis, and [4] lower baseline LH levels (59). Since not all men will admit to T use, those with an LH <0.06 IU/L should be questioned about exogenous T exposure (60).

Stopping T replacement therapy is the first step for those men pursuing fertility; 50% of patients will have normal T within 6 months, and nearly all (95%-98%) will normalize within 15–18 months (59). If T levels do not respond adequately, or if a more rapid return to testicular function is desired, adding hCG, CC, or AIs has been suggested. When initiating hCG replacement, the goal of a 400–800 ng/dL T level may require an SC hCG dose between 500 and 10,000 units every other day (3 times per week). A suboptimal hCG response may result from a history of cryptorchidism or the development of hCG antibodies (61, 62). Once the total T level has normalized, a semen analysis with a concentration over 15 M/mL will typically take 6–24 months (63). If the concentration is not over 5–7 M/mL by 6–12 months, consider adding hMG or another FSH product to the treatment plan.

There are men who report “feeling bad” off exogenous T in spite of CC stimulation. For these, consider stimulating testicular function using low-dose hCG while continuing exogenous T replacement (64). Hsieh et al. suggest using hCG concurrent with T replacement therapy to maintain both testicular size and spermatogenesis (65).

Pentoxifylline and Trental

Pentoxifylline (PF) is a methylxanthine derivative that interferes with the metabolism of cyclic adenosine monophosphate (cAMP) by inhibiting phosphodiesterase and thereby increasing cAMP levels. Increased cAMP levels have resulted in both improved acrosome reactions (66) and sperm motility (67). On its own, PF administration had demonstrated improvements in microcirculation by both increasing erythrocyte deformability and decreasing both blood viscosity and platelet aggregation (68). Improving microcirculation may combat the association between idiopathic male factor infertility and decreased testicular perfusion (68). Moreover, PF exhibits antioxidant properties by inhibiting interleukin-6 activation of leukocytes and by inhibiting xanthine oxidase, thereby reducing intracellular oxygen free radicals (66). Interestingly, free radicals are necessary for normal sperm function; however, at high levels, reactive oxygen species damage sperm membranes and DNA integrity. Moreover, increased lipid peroxidation can result in decreased membrane fluidity, which can lead to low sperm motility and impairment of important functions such as the acrosome reaction. PF has been shown to exhibit antioxidative functions and radical scavenging properties, both of which have improved sperm motility, enhanced the acrosome reaction, and increased the proportion of hyperactivated spermatooza (69, 70).

PF was first used to improve fertilization in vitro, after which it was used in oocyte micromanipulation as well as IUI. In vitro treatment of sperm with topically applied PF led to increased sperm motility, enhancement of acrosome reaction, increase of sperm penetration, and protection of the sperm plasma membrane. Rizk et al. demonstrated a higher fertilization rate (45 of 49 cycles, 92%) in the cohort where oocytes were inseminated with PF-treated spermatooza compared with controls (P<.05). The study suggested that PF improved the fertilization rate and outcomes in couples with male factor infertility and poor fertilization rates (71).

Orally administered PF has been studied as a way to improve testicular blood flow while mitigating sperm oxidative stress. Safarinejad reported a significant increase (from baseline) in sperm concentration (26.4 vs. 16.2 M/mL), motility (35.8% vs. 26.4%), and normal morphology after PF administration in patients who underwent double blind therapy with 400 mg of PF (all P=.001). This same study also demonstrated increased acrosome reactions observed in the PF-treated cohort (66). Other enteral PF studies were unable to demonstrate meaningful PF responses, resulting in conflicting evidence for its usefulness (68, 72, 73).

The recommended oral dose is 400–600 mg 3 times a day for 3–6 months. This highly hydrosoluble drug is rapidly and extensively absorbed from the gastrointestinal tract and uniformly distributed throughout all body tissues—including the genital tract and its secretions (68).

Use of PF has received much attention for its role in the treatment of male factor infertility. On the one hand, PF continues to be used in vitro as an effective way to improve sperm motility. On the other hand, orally administered PF for the treatment of idiopathic male factor infertility has not been as successful. A review of published data was not able to support a beneficial role for the systemic use of PF in idiopathic male factor infertility (68).

CONCLUSION

Treating the 50% of infertile men with idiopathic infertility is a vexing problem with limited options. Treatment options include EMTs. Unfortunately, the use of these off-label pharmaceuticals has both varied and unreliable results. Future studies using these medications should clarify optimal treatment regimens and pregnancy-related outcomes.

Acknowledgment: The gonadotropin section was adapted from reference (19).

REFERENCES


