Commentary On Phosphodiesterase Type 5 Inhibitor Therapy for Sexual Dysfunction Induced by Male Infertility

Bruce R. Gilbert, MD, PhD
Associate Clinical Professor of Urology, Weill Cornell Medical College, New York, New York

It is not uncommon for the male partner of an infertile couple to be unable to produce a semen specimen on the day of his partner’s in vitro fertilization (IVF) procedure. This was highlighted in a study by Saleh and colleagues. In their study, 46 (11%) of 405 men were unable to produce a specimen for analysis after two to four attempts on two separate occasions at 2- to 3-day intervals. All 46 men also experienced problems with erection or orgasm and had severe anxiety during attempts to masturbate as well as during sexual contact with their partners. This inability to produce a specimen on demand has been referred to as temporary, secondary, or situational erectile dysfunction. With time of the essence and often substantial out-of-pocket costs, the inability to produce a specimen at the scheduled time of the in vitro fertilization procedure often results in a request to the urologist for urgent surgical sperm retrieval.

The psychological stress of an infertility diagnosis resulting in erectile dysfunction has been studied. Mongo and colleagues compared 18 infertile couples to 12 couples seeking elective sterilization using the International Index of Erectile Function (IIEF); the infertile male partners had significantly lower IIEF scores than the males seeking elective sterilization. In addition, Beutel and colleagues found a direct correlation between the male stress factor and the degree to which he feels responsible for the couple’s infertility. In addition to the effect of stress on erectile function, growing evidence documents a significant effect of psychological stress on semen quality and fecundity.

Psychological Stress
Clarke and colleagues demonstrated a significant inverse relationship between sperm motility and the perceived importance of producing a semen specimen. Danish couples attempting pregnancy for the first time (n = 430) were evaluated for psychological stress by Hjollund and colleagues using a validated instrument (General Health Questionnaire). Data were collected to determine sperm density and several hormonal variables. No consistent associations were found between stress and serum concentration of luteinizing hormone, follicle-stimulating hormone, inhibin B, testosterone, or estradiol. The fecundity rate was significantly lower in men with sperm density less than 20 million/mL when comparing the highest-distressed quartile to the lowest-distressed quartile in this low-sperm-density group.

The widespread availability of oral agents for the treatment of sexual dysfunction has encouraged several researchers to use sildenafil citrate in men with situational erectile dysfunction. The first reported successful use of sildenafil citrate was by Tur-Kaspa and colleagues who gave the drug to a man who could not produce a specimen for the couple’s first in vitro fertilization procedure after trying for 12 hours. The man had not had problems in providing sperm samples during previous intrauterine insemination cycles. Kaplan and colleagues gave sildenafil to ten men with previously normal sexual function who were unable to produce a specimen for a stimulated cycle of intrauterine insemination. Six patients (60%) were able to achieve an erection and ejaculation with a 50-mg dose, whereas two others needed a 100-mg dose. Two patients (20%) were
unable to ejaculate with either a 50-
mg or 100-mg dose. The article by
Jannini and colleagues describes an
uncontrolled, open-label pilot study
in which a group of sexually healthy
men (as indicated by the validated
IIEF questionnaire), were given sildena-
afil 50 mg, before intrauterine insemi-
nation (n = 25) or planned intercourse
for a postcoital test (n = 12).10 Before
treatment with sildenafil, seven of the
25 patients (28%) attempting to pro-
duce a specimen for intrauterine
insemination and five of the 12 during
couitus (47%) had some degree of erec-
tile dysfunction (as documented by a
modified IIEF, patient log, or both).
With sildenafil all patients had both
subjective and objective improvement
in their erectile function.

Clinical Data on Sildenafil
Sildenafil is found in semen, as
stated in pharmaceutical companies’
package insert. Therefore, the poten-
tial effects of sildenafil citrate and its
metabolites on sperm quality and
function, the female genital tract, fer-
tilization, implantation, and embryo
development must be known before
advocating use of this drug in couples
attempting conception. The Table lists
an overview of some of the human
and in vitro studies that have exam-
ined the effect of sildenafil on process-
es other than erectile function.

Human Studies
In the group producing a specimen
for intrauterine insemination Jannini
and colleagues10 found no significant
change in ejaculated volume, sperm
number, or nonlinear progressive
motility. They did, however, find a
significant increase in linear progres-
sive motility. Two of the 25 couples
undergoing intrauterine insemination
conceived. When sildenafil was given
before a second postcoital test ther e
was an increase in both the total num-
ber of spermatozoa and the linear
progressive motility. The authors con-
cluded that use of sildenafil decreased
psychological stress associated with

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Total Count</th>
<th>Motility</th>
<th>Morphology</th>
<th>Viability</th>
<th>Acrosome Reaction</th>
<th>Capacitation</th>
<th>Zona Pellicuda Binding</th>
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<tbody>
<tr>
<td>Jannini et al10</td>
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<td>↑</td>
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<tr>
<td>Purvis et al11</td>
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<tr>
<td>Aversa et al12</td>
<td>Human</td>
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<tr>
<td>du Pleisses et al13</td>
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<td>0</td>
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<td>↑</td>
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<tr>
<td>Burger et al14</td>
<td>In vitro</td>
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<td>0</td>
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<td>—</td>
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<tr>
<td>Cuadra et al15</td>
<td>In vitro</td>
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<td>↑/↓</td>
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<td>↑</td>
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<tr>
<td>Lefievre et al16</td>
<td>In vitro</td>
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0, no change; ↑, increased; ↓, decreased; ↑/↓, increased at low concentration and decreased at higher concentration.

Unfortunately, no validated instru-
ment was used to measure psychological
stress.

Purvis and colleagues11 conducted
a randomized, double-blind, placebo-
controlled, 2-way crossover study in
17 healthy male volunteers (age 19-
34 years) to evaluate the effects of
sildenafil (100-mg single dose) on
sperm variables. Volunteers each
received a single dose of sildenafil for
two periods and a single dose of
placebo for two periods with each
period separated by a washout period
of at least 5 to 7 days. Semen and
blood samples were obtained to assay
sildenafil and metabolite concentra-
tions. They found that sildenafil did
not have statistically significant
effects on sperm motility, count, den-
sity; the percentage of abnormal
sperm forms; or the percentage of liv-
ing sperm. Nor did it alter the volume
or viscosity of the semen. The mean
semen concentrations of sildenafil at
1.5 and 4 hours post dose were
approximately 18% of the plasma concentrations at the same points in time and the concentrations of the sildenafil metabolite were 5% and 15% at the same point in time. These observations were similar to those of Aversa and colleagues who conducted a prospective, randomized, double-blind, placebo-controlled, 2-period crossover study, and found no significant differences between treatment groups for sperm number, motility, and abnormal morphology.12

The du Pleisses study group investigated the effects of acute in vivo sildenafil and in vitro 8-bromo-cyclic guanosine monophosphate (8-Br-cGMP) in a prospective, double-blind, placebo-controlled, crossover, 2-period clinical study.13 The investigators found no effect on macroscopic and microscopic seminal variables or on the acrosome reaction. Sperm-zona pellucida binding results were increased to 148.75% and 134% with the treatment of sildenafil and 8-Br-cGMP, respectively.

These human studies therefore do not clearly demonstrate an effect of sildenafil on sperm motility. However, they do confirm significant concentrations of sildenafil in semen and the effect of sildenafil citrate on sperm-zona pellucida binding.

In Vitro Studies

Burger and colleagues found that sildenafil, at doses of 125, 250, and 750 ng/mL, did not significantly alter the motility, viability, membrane integrity, or sperm penetration characteristics of human spermatozoa from normal donors (n = 6) and infertile patients (n = 6; motility 30%, forward progression <2, and viability <50%).14 Washed sperm were incubated with sildenafil (125, 250, and 750 ng/mL), pentoxifylline as a positive control, and Ham’s F-10 medium as a reagent control. Sperm were exposed to the highest possible concentrations of sildenafil as they traversed the testis, seminal vesicle, and prostate. No significant change in motility was observed between sildenafil incubation and control and no significant change in viability from normal donors was observed up to 3 hours. At 1 hour, however, sperm from infertile patients incubated with sildenafil 125 and 750 ng/mL had significantly lower viability than Ham’s control and pentoxifylline samples. This may be important if sildenafil were to be used by subfertile couples with a male factor.

Cuadra and colleagues studied the effect of sildenafil on sperm motility and acrosome variables.15 Specimens were obtained from a proven donor. Sperm were incubated at 37°C for 48 hours in solutions of sildenafil at concentrations of 0 (control), 0.4, 4, and 40 nmol/L, which are thought to approximate semen and plasma levels of sildenafil. Motility variables were increased at low concentrations of sildenafil but decreased at higher concentrations when compared with the control. In addition, motility decreased as the sildenafil dose increased over 48 hours. At all concentrations tested, sildenafil stimulated sperm acrosome reaction by approximately 50% above control. The acrosome reaction is required for spermatozoa to penetrate the sperm-zona pellucida; however, the effect sildenafil might have on fertilization is not known.

Lefievre and colleagues investigated whether phosphodiesterase type 5 inhibitor (PDE-5) is present in sperm by assessing whether sildenafil affects sperm function.16 Washed sperm were incubated with increasing concentrations of sildenafil or dipyridamole, another selective inhibitor cGMP–specific PDE-5, and PDE-5 activity was assayed. Both sildenafil and dipyridamole inhibited sperm PDE activity; when cGMP was used as a substrate, sildenafil was four times more potent than dipyridamole at inhibiting PDE-5. No difference was noted when cyclic adenosine monophosphate (cAMP) was used as the substrate. When sperm were treated with 100- or 200-µM sildenafil citrate there was a time-dependent increase in curvilinear velocity, amplitude of lateral head displacement, and hyperactivation, but no change in linearity. Sildenafil citrate at 30-, 100-, and 200-µM triggered sperm capacitation. Capacitated sperm (but not sperm incubated in noncapacitating conditions) underwent an acrosome reaction when challenged with lysophosphatidylcholine (LPC) alone or LPC plus PDE-5, but not with sildenafil or another PDE-5 alone. This ability of sildenafil to trigger capacitation outside the female
genital tract might have clinical significance. Therefore, sperm stored in the male genital tract may undergo capacitation before ejaculation, possibly resulting in senescent sperm with a decreased fertilizing ability.

Results from these in vitro studies suggest a biphasic effect of sildenafil on sperm motility. At low concentrations of sildenafil, motility appears to be enhanced; at higher concentrations, a decrease in sperm motility was observed. The stimulating effect of sildenafil on the acrosome reaction, capacitation, and sperm-zona pellucida binding is interesting and certainly requires further clinical investigation to identify what effects sildenafil might have on human reproduction.

The physiologic effects of vaginal sildenafil exposure are not known. Purvis and colleagues demonstrated that the concentration of sildenafil in semen was approximately 18% of that found in plasma 1.5 to 4 hours after the dose. In a retrospective cohort analysis, Sher and Fisch have shown that vaginal suppositories of sildenafil increase both uterine artery blood flow and endometrial development. Paulus and colleagues, in a flow and endometrial development analysis, Sher and Fisch have shown the dose. In a retrospective cohort analysis, Fisch, found a significant increase in the effects of sildenafil citrate on the female genital tract as well as on fertilization, implantation, and embryo development must be known. Until the effects of sildenafil citrate on the various stages of sperm-oocyte interaction are understood, caution is indicated in its use in couples attempting conception.

Conclusion

The use of an oral agent for men with situational erectile dysfunction appears simple, effective, and certainly less invasive than surgical retrieval. However, sildenafil citrate appears to affect more than just erectile function. Rigorous clinical studies are needed to demonstrate that its use does not adversely affect sperm quality or function. In addition, since sildenafil citrate is excreted in the semen, the effects of sildenafil citrate on sperm motility were enhanced; at higher concentrations, a decrease in sperm motility was observed. The stimulating effect of sildenafil on the acrosome reaction, capacitation, and sperm-zona pellucida binding is interesting and certainly requires further clinical investigation to identify what effects sildenafil might have on human reproduction.

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References


Disclosure: Dr. Gilbert is on the Speaker’s Bureau for Pfizer, Inc.