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

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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.[1-3] This was highlighted in a study by Saleh and colleagues.[4] 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.

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The psychological stress of an infertility diagnosis resulting in erectile dysfunction has been studied. Mongo and colleagues[5] 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[6] 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[7] 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).[8] 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[1] 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.[9] 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 sildenafil 50 mg, before intrauterine insemination (n = 25) or planned intercourse for a postcoital test (n = 12).[10] Before treatment with sildenafil, seven of the 25 patients (28%) attempting to produce a specimen for intrauterine insemination and five of the 12 during coitus (47%) had some degree of erectile 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 potential effects of sildenafil citrate and its metabolites on sperm quality and function, the female genital tract, fertilization, 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 examined the effect of sildenafil on processes other than erectile function.

Human Studies

In the group producing a specimen for intrauterine insemination Jannini and colleagues[10] found no significant change in ejaculated volume, sperm number, or nonlinear progressive motility. They did, however, find a significant increase in linear progressive motility. Two of the 25 couples undergoing intrauterine insemination conceived. When sildenafil was given before a second postcoital test there was an increase in both the total number of spermatozoa and the linear progressive motility. The authors concluded that use of sildenafil decreased psychological stress associated with fertility evaluation and treatment. Unfortunately, no validated instrument was used to measure psychological stress.

Purvis and colleagues[11] 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 concentrations. They found that sildenafil did not have statistically significant effects on sperm motility, count, density; the percentage of abnormal sperm forms; or the percentage of living 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

Table

Significant Changes in Semen Variables and Sperm Function Found in Various Studies

		Semen Variables and Sperm Function						
	Study Type	Total Count	Motility	Morphology	Viability	Acrosome Reaction	Capacitation	Zona Pellucida Binding
Jannini et al[10]	Human	0	↑	—	—	—	—	—
Purvis et al[11]	Human	0	0	0	—	—	—	—
Aversa et al[12]	Human	0	0	0	—	—	—	—
du Pleisses et al[13]	Human	0	0	0	—	0	—	↑
Burger et al[14]	In vitro	0	0	0	↓	—	—	—
Cuadra et al[15]	In vitro	—	↑/↓	—	—	↑	—	—
Lefievre et al[16]	In vitro	—	↑	—	—	↑	↑	—

0, no change; ↑, increased; ↓, decreased; ↑/↓, increased at low concentration and decreased at higher concentration.

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.

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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[11] 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.[17,18] Paulus and colleagues, in a study similar to the one by Sher and Fisch, found a significant increase in endometrial thickness after sildenafil citrate administration.[19] The suppositories used in these studies were compounded by a local pharmacy from tablets, and neither vaginal nor plasma concentrations were measured to be able to assess the absorption or bioavailability of sildenafil in their preparation. Nonetheless, the measured change in uterine blood flow and endometrial development documents a nontrivial effect of sildenafil citrate through vaginal exposure.

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 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. ■

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