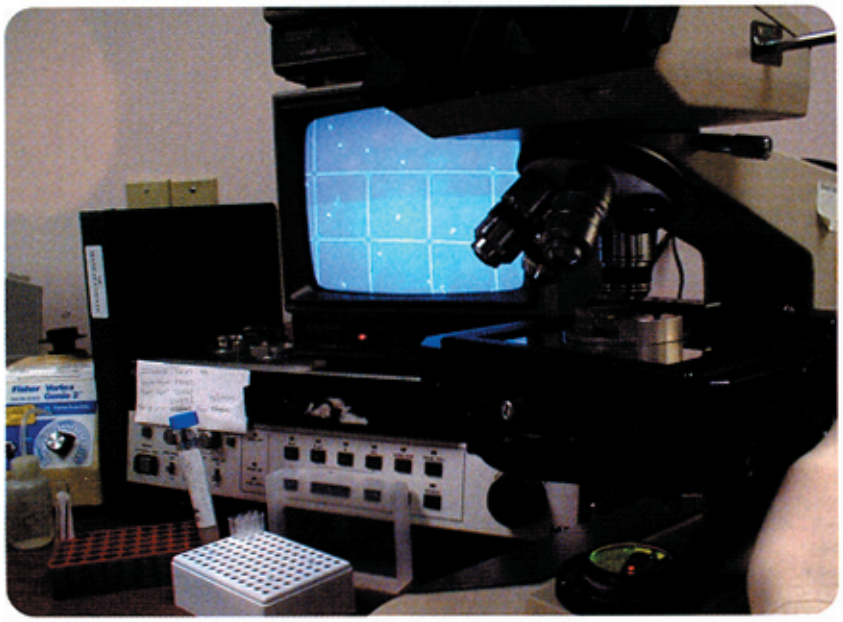
Evaluating the infertile male—Part 1

By Sherman J. Silber, MD

An expert in infertility and microsurgery explains how to interpret semen analysis in Part 1 of a two-part series on male infertility. He also tells why much traditional treatment of male infertility—including varicocelectomy—is pointless.



What causes male infertility and what's the best way to treat it? The debate has raged on for decades. Among the many treatments strongly advocated over the past 40 years are clomiphene citrate; testosterone; human menopausal gonadotropin; human chorionic gonadotropin; corticosteroids (for sperm antibodies); cold, wet athletic supporters; and worthless nutritional supplements—but there's no evidence that any of these are effective.[1] We've even begun to seriously question the efficacy of varicocelectomy.[2-6] The bottom line: Most spermatogenic defects are actually genetic in origin and clearly impervious to improvement with any therapy.[7-11]

My goal here is to debunk some of the myths still surrounding male infertility, discuss the latest treatment options, and present our most current understanding. In Part 2 of this article, I'll more thoroughly cover sperm retrieval and intracytoplasmic sperm injection (ICSI), which has now

DR. SILBER, a pioneer in microsurgery and infertility, is a leading authority on IVF, egg and embryo freezing, sperm retrieval, and ICSI. He performed the world's first microsurgical vasectomy reversal and the first testicle transplant and the world's first ovary transplant. The author of four best-selling books for the layman as well as 250 scientific papers on infertility and reproduction, he is Director of the Infertility Center of St. Louis, St. Luke's Hospital, St. Louis, Mo.

TABLE 1

Frequency distribution of motile sperm count and pregnancy rates post-vasovasostomy in men whose wives did or did not become pregnant (10-year follow-up)

Total motile sperm count (10^6/ejaculate	0–10	10–20	20–40	40–80	>80	Totals
Total patients (frequency distribution)	32 (12%)	31 (12%)	32 (12%)	79 (31%)	84 (33%)	258 (100%)
No. pregnant (frequency distribution)	25 (11%)	27 (12%)	30 (13%)	68 (30%)	78 (34%)	228 (100%)
Pregnancy rate	78%	87%	94%	86%	93%	88%

Source: Adapted from Silber SJ.[15]

become the most effective approach for even the most severe cases of male infertility.[12]

Evaluating the male

Even though sperm count is still the key test for evaluating the male, a poor semen analysis, or a low sperm count, doesn't rule out natural conception. Nor does a normal sperm count guarantee that a husband's sperm will fertilize his wife's eggs. Men with extremely low sperm counts often have no problem impregnating their wives, whereas no fertilization takes place in a small percentage of in vitro fertilization (IVF) cycles in which the semen analysis is totally normal.[1,13,14]

Does sperm count correlate with spontaneous pregnancy rate?

Table 1 compares motile sperm counts in men following vasovasostomy (vasectomy reversal) whose wives became pregnant to those whose wives did not conceive. Note that in both groups the total motile sperm per ejaculate hardly differed at all.[15,16] As for the "successful" vasovasostomy patients whose wives became pregnant, 12% had total motile sperm counts per ejaculate of less than 10×10^6. In fact, in a comprehensive comparison, Jouannet and colleagues found that above 5×10^6 sperm, the difference in pregnancy rate is not convincingly related to differences in sperm count.[17]

That said, although a low sperm count and low sperm motility don't necessarily indicate infertility in any particular couple, controlled studies have shown that lower motile sperm counts are still associated with lower spontaneous conception rates over time in infertile couples. In 1983, investigators showed that even with no treatment, if the motile sperm count was below 1×10^6/mL (even as low as 100,000/mL), there was a 4% spontaneous pregnancy rate within 5 years and a 9% rate within 12 years.[18]

Shortly after that, one researcher constructed a pregnancy curve for infertile couples having varying degrees of oligozoospermia, comparing them to various fertile control populations.[19-22] Again, quite remarkably, even with fewer than 5×10^6 spermatozoa/mL regardless of motility, the pregnancy rate at 2 years was 26% (Figure 1). Thus, even though it's possible for spouses of men with extremely low sperm counts to spontaneously conceive, a higher motile sperm count does increase the odds of doing so.

Actually, the sperm count isn't the major variable in determining the oligospermic couple's chances for pregnancy—it's the wife's fertility. A severely oligospermic man might succeed in impregnating his wife even given his very small number of spermatozoa if the wife herself did not also have reduced fertility.[15] In fact, the most critical factors that determined pregnancy prognosis in oligospermic couples—more so even than the sperm count—were the wife's age and the duration of previous infertility.[23,24]

One group of investigators found that treating varicocele and sperm count had little effect on the pregnancy rate. Both these and other researchers have shown that the wife's age is the single most important determinant of the couple's fertility.[2,3,25] Nonetheless, depressed sperm parameters do affect a couple's fertility.

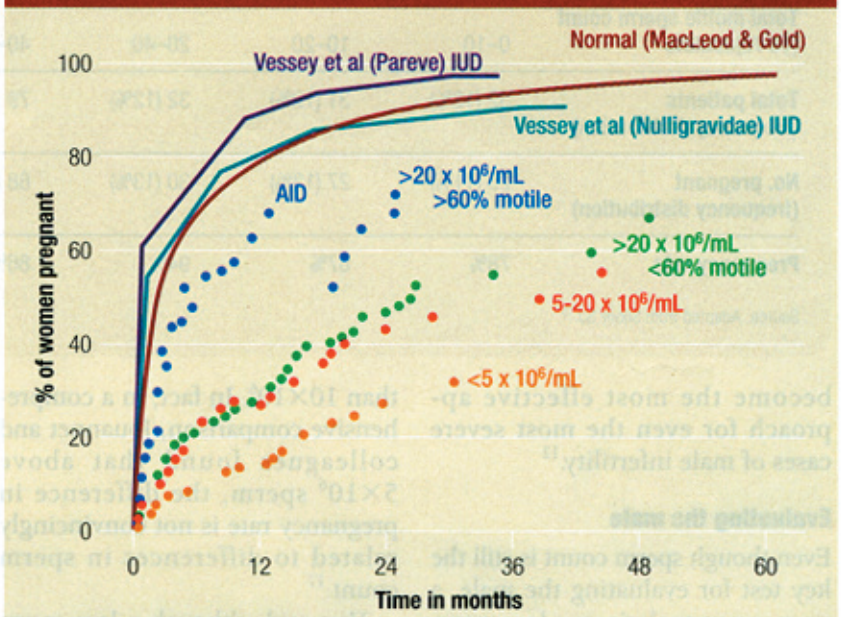
Zona binding, sperm penetration, and IVF

Fertilization failure is unexplained in at least one of every four cases. To find out why, Liu and Baker

Take-home Messages

- Counsel patients that sperm retrieval and intracytoplasmic sperm injection (ICSI) is now the most effective therapy for even the most severe cases of male infertility. Steer them away from many widely advocated but useless treatments like nutritional supplements.
- Skip the expensive sperm function tests and stick with routine semen analysis with morphology and motility assessment—but take its limitations into account.
- Be aware that while many urologists swear by varicocelectomy for treating male infertility, most other infertility specialists view that approach with skepticism, seeing it as a waste of a couple's limited biological time.

FIGURE 1. Cumulative and lifetable pregnancy rates in couples with varying sperm counts



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extensively studied the sperm of patients with unexplained "failed fertilization" in IVF who otherwise had completely normal semen parameters, including normal semen counts.[26-29] They found that when there was fertilization failure (1) sperm with abnormal morphology did not bind to or penetrate the zona pellucida, and (2) sperm with normal morphology did bind to the zona pellucida, but could not penetrate it. A failure of the zona-induced sperm acrosome reaction may thus explain the failure of fertilization in men with otherwise normal semen parameters. General "acrosome reaction" assays that are not induced by zona-binding are unphysiologic and, therefore, it's not surprising that they have no predictive value.[30] They are irrelevant to how a sperm fertilizes an egg, which, of course, begins with the zona-induced acrosome reaction. Thus, the studies by Liu and Baker seemed to clear up much confusion about sperm testing problems, offer an explanation for unexplained failed fertilization, and also for why and how a sperm's shape affects fertility.[31]

It is probably the diverse population of spermatozoa in the semen of each male that makes such testing problematic, as most infertile men who are not azoospermic represent a spectrum of fertility. The development of IVF and ICSI, and the unreliability of semen analysis in providing prognostic information to predict fertilization, led to the proliferation of all of these more complicated and expensive sperm function tests. But most clinicians today favor only routine semen analysis

with morphology and motility assessment, at the same time recognizing full well its limitations.[32,33]

Conventional treatment of male infertility

For the most part, treatment of male infertility before IVF and ICSI had been "authority-based," and not "evidence-based." I seriously doubt whether any treatment whatsoever can improve the fertility of any male with oligospermia, or oligoasthenoteratospermia (defined as low sperm count, low motility, and abnormal morphology), be it anti-estrogens like clomiphene citrate and tamoxifen, androgens, gonadotropins, or even varicocelectomy.[1-7,34-36] Some argue that with the exception of an occasionally detected testicular cancer, even physical examination has no impact on therapeutic results for oligoasthenoteratospermia.[36]

The most controversial subject in the area of male infertility is probably varicocele. Most nonurologist infertility specialists around the world are extremely skeptical of the role of varicocelectomy in treating male infertility, despite the fact that most urologists are enthusiasts. The directors of most ART programs view the enthusiasm with which urologists approach varicocelectomy as a potential impediment to the couple that is getting older and often do not have much time left for having good pregnancy rates with ART.

The only "controlled" studies that favored varicocelectomy were extremely flawed by patient selection. One study involved 455 pa-

tients undergoing varicocelectomy with only 19 controls.[37] Another study involved 1,500 infertile men who underwent varicocelectomy and only 47 controls.[38] Yet another controlled study involved a subset of 238 couples who were split off from the original WHO study of more than 7,000 couples. Of these, only 45 were actually studied and the remaining 193 were unavailable.[2,3,39] Thus, the evidence in favor of varicocelectomy for male factor infertility is quite poor.

Don't be fooled into thinking that the sperm count has gone up after varicocelectomy, because careful studies of semen analysis in untreated patients over time often seem to increase due to the statistical phenomenon known as "regression toward the mean."[40] Whenever an extremely variable test result (like semen analysis) is measured, the phenomenon of "regression toward the mean" will make it appear that a patient who initially sees a specialist due to a low sperm count will appear over time to improve with no treatment at all. By the same token, if a patient is initially found to have a very high sperm count, it will appear over time to go down. First recognized in a study by MacLeod and Gold in 1951, regression toward the mean was mathematically elucidated with carefully controlled longitudinal trials in 1985.[41] And it now serves as a model for evaluating the countless ineffective treatments for male infertility that have been mistakenly advocated.[23,40,42-48]

As we've seen, the number and quality of sperm a man needs to be fertile is a complex question. Until IVF and ICSI came along, the treatment of male infertility was far from evidence-based. Actually the basic semen analysis may still be the cheapest and most effective approach for evaluating the male. By separating the evidence from the myths about treating male infertility, we can help prevent patients from wasting precious time on worthless approaches. □

Editor's note: In Part 2 of Dr. Silber's article next month, he delves deeper into the genetic origin of most spermatogenic defects and covers modern techniques like MESA and ICSI.

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OCTOBER 2004 ■ VOL. 49, NO. 10

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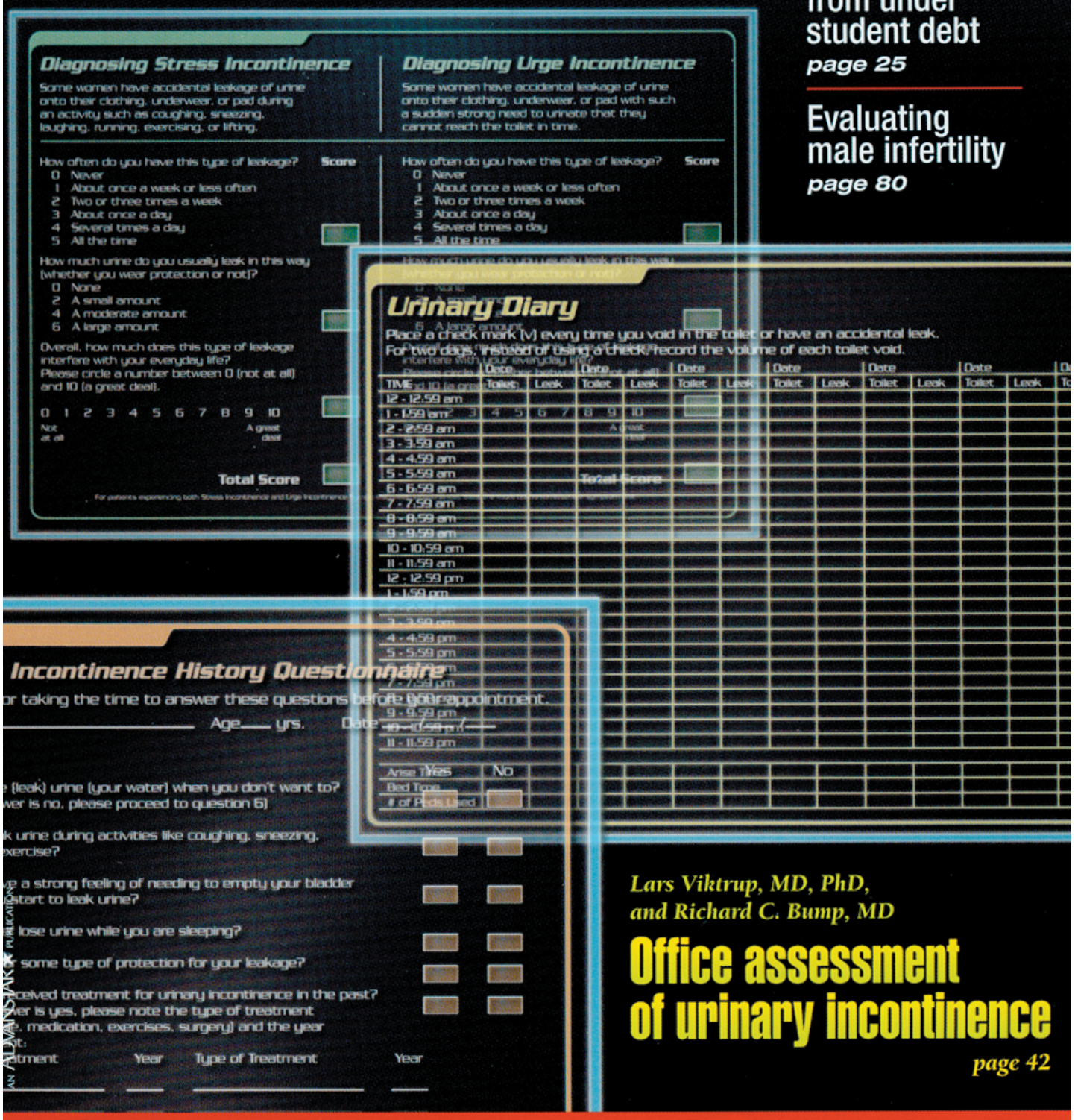

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