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Vasectomy Reversal in the Presence of Diminished Ovarian Reserve: A Complex Clinical Conundrum

Androlog Summary

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Clinical reproductive practice is often multivariate: multiple conditions in the male and/or female may coexist to confound diagnoses and therapeutic strategies. Given that treatment of an underlying condition in the male may be bypassed by extraction of sperm and intracytoplasmic injection (ICSI), the therapeutic choices in a multivariate clinical problem may become quite confusing for the physician and for the couple. Such is the case with a man who has had a vasectomy and a woman with diminished ovarian reserve. Should the surgeon proceed with vasectomy reversal and the reproductive endocrinologist use donor ova? Or natural cycles? Or should testicular sperm extraction be used with donor ova, or with the patients own ova? Jay Sandlow asks:

> I was wondering what the experience has been in performing vasectomy reversals in men who have partners with either diminished ovarian reserve or elevated day 3 FSH levels. The reproductive endocrinologists typically recommend donor eggs (which most couples are adverse to), especially if the woman is older. However, many of these women have regular monthly cycles and ovulate based on home ovulation kits. Has anyone had a successful pregnancy in this setting (either abnormal clomiphene challenge test and/or elevated day 3 FSH)? I would appreciate the group's thoughts. Thanks.

Eric Seaman echoes a similar case in his practice, and relates that the woman became pregnant with her own ova before donor ova were utilized:

> The question actually relates to one of my first reversals in practice. I asked the patient about his wife prior to performing the reversal and he confirmed that there were no fertility concerns on the wife's side; however, a few months after surgery (with a good postop semen analysis), further gyn evaluation revealed evidence of premature ovarian failure as manifested by elevated FSH and the couple was counseled to pursue donor eggs. Prior to initiating the donor cycle, protocol for this RE group was to administer a pregnancy test, and, sure enough, she was pregnant! I was then informed behind the scenes that pregnancy in this setting (of POF) has a high miscarriage rate. However, 9 months later, a healthy baby was born.

Peter Schlegel describes the problem in accurately assessing outcomes of both artificial reproductive techniques and natural conception, making this particular multivariate problem especially perplexing:

> Dr Sandlow has raised an interesting question regarding women with reduced ovarian reserve (also applies to older women). Abnormal ovarian reserve testing is a relatively effective prognostic factor to predict a woman's response to ovarian stimulation. Its relationship to natural fertility is not well understood. In addition, it is difficult to measure (eg, for a 43-year-old woman), whether a 5%–10% chance of pregnancy with IVF is better than a 1%–3% chance per month of natural pregnancy (eg, after vasectomy reversal). Data on this subject are limited, in my recent reviews, but I'd be happy to see if others have more information.

Eugene Fuchs notes the overall poor outcome for women of advanced age and attendant diminished ovarian reserve:

> Jay Sandlow's question about performing vasectomy reversal on men who have partners with diminished ovarian reserve is an excellent one. I have had concern about this for years and currently strongly advise a clomid challenge test for most women over 35, especially if they have not had a pregnancy within a few years, which is most often the case. As you might expect, many, but not all, of these couples in my experience will still go forward with the reversal when they have every indication of diminished ovarian reserve. This is not a tracking point in my data base but I believe there has not been a pregnancy. Only about 20% of women over age 40 will conceive after a partner's vas reversal has been technically successful. This is what we found in our cohort and published a few years ago in *Fertility and Sterility*. I look forward to other thoughts.

Paul C. Magarelli, a Reproductive Endocrinologist, describes a statistical basis for addressing this particular multivariate clinical problem:

> 1) What are the chances of intercourse achieving a live birth (not simply a pregnancy) in women with diminished ovarian reserve? 2) Your concern for vas reversal or ICSI.
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> If we utilize our general understanding of reproductive medicine, women in their 20s have a 20% chance per month of pregnancy with intercourse (IC) versus 50%–60%

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change with IVF and ICSI (testicular sperm). If a woman is 30, the chance for pregnancy is 10%/month with IC and 40% with IVF and ICSI (testicular sperm). At 40, this chance changes to 4% with IC and 20%–30% with IVF and ICSI (testicular sperm). If we then add to this diminished ovarian reserve, then based on the FSH or clomid challenge test for ovarian reserve, the numbers for IC fall almost to 0, while the numbers for IVF may reach 20%–25%.

So, when counseling patients, I would review the stats and let them decide.

Jeff Persson argues for vasectomy reversal based on increasing the probability by increasing the number of opportunities available for conception:

I have treated a few couples in this scenario of a probably diminished ovarian reserve and I think it makes more sense to offer vasectomy reversal rather than IVF. In women with a diminished ovarian reserve, the likelihood that any particular oocyte cohort is collected for IVF treatment suitable is clearly diminished, yet with natural conception opportunities, in each cycle, there must clearly be a reasonable chance that the fertile oocyte can be fertilized in vivo. I believe that, in older women or women with a diminished ovarian reserve, vasectomy reversal makes better sense but I can't prove it. For the same reason, I think it makes more sense to offer a focus upon natural fertility rather than using IVF in women over the age of 42.

Mark Jutras also argues for vasectomy reversal first:

As a reproductive endocrinologist, I would say it makes more sense to try the vasectomy reversal than to go to donor eggs. You are under no time constraint here and if she does not conceive in 2 or 3 years, she can still do donor egg IVF. I have had women in their 40s who were not candidates for traditional IVF (that is not using donor egg), who delivered after I found a way to avoid IVF. One in particular was 42 with FSH in the 20s, who delivered after tubal anastomosis. She had had 4 failed IVF cycles before this. Somehow, most REs have forgotten that people can conceive without IVF. I have to say, I am surprised at how many couples with young wives are referred to me by urologists for IVF with a relatively short interval from vasectomy (8 years or less).

Juan G. Alvarez summarizes the therapeutic possibilities, and weighs each:

Dr. Sandlow addresses a very important question concerning the best strategy to follow in couples in which the male had a vasectomy and the female has low ovarian reserve. We have seen several cases of couples in which female age ranged between 30 and 36 years, ovarian reserve was low, and where the male partner had a vasectomy performed less than 10 years ago. In 1 of these cases, the couple had undergone ICSI with testicular sperm in a reputable IVF clinic and no pregnancy was achieved after 3 cycles. The couple, advised by their infertility specialist, decided to do vasectomy reversal and cycles of IUI without ovarian stimulation. After 4 cycles, they achieved a pregnancy.

There are 3 main issues that should be considered when facing this dilemma (which would also apply to women >42 years of age with low ovarian reserve):

1. Ovarian reserve

Would ovarian stimulation and TESE-ICSI help these couples in achieving a pregnancy or would it accelerate oocyte depletion? Scientific evidence suggests that the quality of an oocyte from a natural cycle is better than that obtained after ovarian stimulation with high doses of rFSH. This would be in favor of doing vasectomy reversal and timed intercourse (or IUI without ovarian stimulation).

2. Quality of testicular vs ejaculated sperm

Recent studies indicate that pregnancy rates using testicular sperm in males with high DNA fragmentation levels in semen are significantly higher than when using ejaculated spermatozoa (Greco et al, *Hum Reprod.* 2005;20:226). DNA fragmention was significantly lower in testicular vs ejaculated sperm. Several studies show that most of this damage occurs posttesticularly during sperm transport through the epididymis. These authors also showed that treatment of these patients with antioxidants significantly reduced DNA fragmentation in ejaculated spermatozoa, suggesting that this DNA damage may be the result of oxidative stress (Greco et al, *J Androl.* 2005;26:349). DNA fragmentation associated to apoptosis and aneuploidy would be mostly likely to occur in cases of severe oligospermia/azoospermia due to partial/total maturation arrest and meiotic alterations during spermatogenesis but unlikely to occur in cases of males with a vasectomy. Because sperm DNA fragmentation increases significantly above 40 years of age and most cases of vasectomy reversal would be contemplated in males above this age, sperm DNA fragmentation in semen should be evaluated in these couples and, if above normal levels, treated.

3. Ovarian reserve and advanced age

Concerning the scenario in women >42 years of age (with their corresponding physiological low ovarian reserve), in a recent study published in Human Reproduction, using a Monte Carlo simulation model, the author found that ART in these women would only marginally contribute (about 3%) toward achieving a pregnancy and recommended natural cycles and timed intercourse (Leridon, *Hum Reprod.* 2004;19:1548). This would also be in favor of doing vasectomy reversal.

Based on these points, whether one strategy or the other would be used is going to depend on how this information is conveyed to the couple and on the couples' priorities. If a pregnancy were not achieved after vasectomy reversal and timed intercourse/IUI, perhaps cycles of oocyte donation with ejaculated spermatozoa should be recommended. This would also favor doing vasectomy reversal.

In reviewing the literature, it is easier to consider the topics of decreased ovarian reserve and advanced maternal age separately.

The efficacy of vasovasostomy (VV) and ICSI declines precipitously in couples with older women. The question ''at what age, if any, does ICSI become superior to VV in postvasectomy couples?'' can only be answered by a prospective trial, which is not available. Instead, the clinician must rely on retrospective series. Two studies in the urologic literature stratified VV cases by maternal age (Fuchs and Burt, 2000; Kolettis et al, 2003). These in-

vestigators found delivery rates of 29%–46% in women age 35–40 and 7%–14% for women above 40. A third study (Deck and Berger, 2000) identified a delivery rate of 17% for all women above 37 years old. Accumulating the data from all 3, an estimate of the rate of delivery for women aged 37+ years would be 14%–25%. In all series, almost all the pregnancies reported occurred in the first 2 years.

ICSI success in postvasectomy cases drops rapidly with advanced maternal age. One study (Nicopoullos et al, 2004) reported live birth rate per cycle of 21% for age 32–37 compared with 10.5% for age >38 in partners of postvasectomy men with ''failed or unfeasible reversal.'' Reanalyzing the data from Abdelmassih et al (2002), we calculate an ongoing pregnancy rate as 16% per cycle (11/67 cycles) for women over age 35. Somewhat surprisingly, these rates are slightly worse than the overall rates for ICSI for all male factor causes reported by SART for the year 2000 (Society for Assisted Reproductive Technology, 2004). After adjusting for the cumulative success rate, assuming 3 cycles per couple (Osmanagaoglu et al, 2002), the overall ICSI success rate becomes 16%–24% for women 38 years or older. Thus, ART offers only a marginal benefit, if any, in this age group, and the morbidity of subjecting both partners to medical intervention must be considered in such a strategy.

Ovarian reserve testing in the form of basal day 3 FSH or clomiphene citrate challenge test is a proven predictor of success with IVF, although its use to exclude patients from IVF programs is controversial (eg, see Abdalla and Thum, 2004). As Dr Schlegel stated in his comments, the applicability of testing outside the ART population is problematic. One recent study investigated the predictive value of FSH testing in healthy females seeking their first pregnancy after age 30 (van Montfrans et al, 2004). No difference in pregnancy rates between patients with elevated FSH and controls was found, although the study has been criticized for being underpowered. It is unfortunately clear that, in women over 40 years old with elevated FSH and a history of female-factor infertility, pregnancy rates without IVF are dismal (4% according to Check et al, 1998). Whether this can be extrapolated to wives of VV patients without a prior history of infertility is very debatable. As Dr Fuchs alluded to in his comments, none of the published VV series tracked FSH as a variable. One surrogate for formal testing is the prior history of the female partner. In a series of 1469 cases (Belker et al, 2003), VV success rates were found to be slightly higher after reversal if the female had been previously pregnant (57% vs 49%, $P = 0.04$). In the Deck and Berger series (2000), all deliveries occurred in women who had been previously pregnant (4/15 cases, or 26%). Thus, in cases with a good history of female fertility, reversal has a reasonable chance of success and appears to be the better choice.

In summary, the literature is lacking on the question of the best strategy in couples with advanced maternal age. Patients should be given a realistic assessment of their chances with either ICSI or VV and let them weigh the morbidities and benefits of each approach. In the case of an abnormal basal FSH test, one must ask why the test was obtained in the first place? Its predictive value depends on whether there is a history suggestive of infertility. Finally, the unfortunate couple with both advanced age and low reserve should be counseled that their chance of genetic offspring with either ICSI or VV is very low and alternative approaches, such as donor gametes, should be seriously considered.

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