Best of the 2013 AUA Annual Meeting Part II

More Highlights From the 2013 American Urological Association Annual Meeting, May 4-8, 2013, San Diego, CA

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KEY WORDS

Male infertility • Exogenous testosterone therapy • MicroTESE • Klinefelter's syndrome • Variocele • Vasectomy reversal • Febrile urinary tract infection • Antibiotic resistance

At the 2013 American Urological Association (AUA) Annual Meeting, held in San Diego, CA May 4-8, 2013, more than 2300 posters, abstracts, and videos were presented. The editors of *Reviews in Urology* have culled an enormous volume of information from this premier source and present those findings that are most relevant to the practicing urologist in Part II of our annual AUA meeting review.

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Male Infertility

In the sphere of male infertility, there are very few studies that rank as Level 1 evidence. Until that occurs, those of us who practice in this domain—and our patients—are left to rely on the "recommendations" of others. Although anecdotal experience is never an acceptable substitute for randomized, blinded, placebo-controlled studies, we are forced to rely on suboptimal "evidence" to help us navigate through this discipline. At the AUA this year, a number of such topics were presented.

Exogenous Testosterone Therapy and Male Infertility

One of the main problems with the use of exogenous testosterone treatment in men is that testosterone

suppresses gonadotropins and, as such, can act like a male contraceptive (ie, it suppresses spermatogenesis). Therefore, the use of exogenous testosterone therapy for the treatment of low testosterone should be used with caution and with the full knowledge of the patient if fertility is still important to them. It is assumed that many physicians who prescribe testosterone are not aware of the association between exogenous testosterone therapy and inhibition of spermatogenesis. Samplaski and colleagues found that 56 patients, or 1.3% of the 4400 patients in their male infertility database, were on exogenous testosterone, and the majority of these patients had their therapy prescribed to them by endocrinologists and family practitioners.[1] The authors suggested that education regarding the association between exogenous testosterone treatment and suppression of spermatogenesis is warranted for these groups of physicians.

Whereas the suppression of spermatogenesis by exogenous testosterone is considered reversible following cessation of treatment, in many instances, patients who have come off their medication may still present to the male infertility specialist with an abnormal sperm count. Purcell and associates found that not all patients who stopped exogenous testosterone therapy in the hope of improving their sperm counts were successful.[2] This would suggest that these patients had the possibility of having a preexisting pathology as the cause of their abnormal sperm counts and, without obtaining a pretreatment sperm count, it will remain unknown whether such pathology exists. Along these same lines, Samplaski and associates found that, after cessation of exogenous testosterone therapy for the treatment of low testosterone, and after excluding those with known diagnoses of testicular pathology (eg, Klinefelter syndrome, Sertoli-cell-only, bilateral undescended testes, Kallmann syndrome, and chemotherapy-induced azoospermia), 80% of such patients will recover spermatogenesis.[3] Indeed, Purcell and coauthors reported a similar 82.4% return of sperm in such patients.[2]

A popular alternative to the use of exogenous testosterone has been the use of estrogen blockers or modulators. Chua and associates identified 11 trials deemed appropriate for analysis.[4] It was determined that the use of these drugs in the indicated population caused a statistically significant increase in testosterone, follicle-stimulating hormone (FSH), pregnancy rates, sperm concentration, and motility when compared with controls, whereas there were no increases in adverse events. Mazzola and colleagues reported that using clomiphene citrate at doses ranging from 25 mg every other day to 50 mg daily resulted in 63% of patients achieving a 200-mg increase of serum testosterone and a total testosterone level of $\geq$ 400 ng/dL with the initial dose.[5] An additional 44% of nonresponders to the initial dose responded upon titration to higher doses of the drug. The only factor predicting response to uptitration was a baseline luteinizing hormone (LH) level; those with an LH level $\leq$ 6 IU/mL responded to the higher doses.

Microdissection Testicular Sperm Extraction

Does every patient who undergoes testicular sperm extraction for supposedly nonobstructive azoospermia require a microdissection testicular sperm extraction (microTESE)? This question arose from the data presented by Mehta and associates.[6] Although this study encompassed a review of a specific group of patients (ie, those with an AZFc microdeletion), the authors found that the only predictor of sperm at retrieval during microTESE was the predominant pattern on prior random testis biopsy. They found that 58% versus 76% versus 100% for Sertoli-cell-only versus maturation arrest versus hypospermatogenesis on a prior random testis biopsy predicted sperm retrieval by microTESE. This begs the original question: should patients with hypospermatogenesis, who have a 100% chance of finding sperm according to these data, undergo a microTESE when a regular TESE may suffice? The concept that microTESE in everyone who has nonobstructive azoospermia may be overkill also can be gleaned from the study by Teloken and colleagues.[7] In this study of patients with testis cancer, 73% of the patients with azoospermia were found to have sperm by regular TESE postorchiectomy. Based on these data, it remains to be determined whether, going forward, the decision to do a microTESE depends on the finding of an initial testis biopsy. This then leads to the obvious conclusion of whether all nonobstructive azoospermia (NOA) patients should then have a testis biopsy in order to determine which of these two procedures should be done at the time of sperm retrieval.

In an attempt to diminish narcotic use post–microTESE, a group at Cornell did a study comparing placebo with celecoxib, 200 mg, by mouth twice daily starting the night before their surgery and continuing for 6 days following surgery. Mehta and associates reported that postoperative narcotic use was significantly less common in the celecoxib group and concluded that celecoxib, 200 mg, twice daily perioperatively and postoperatively is a safe and effective way to

make patients undergoing testicular surgery more comfortable as well as decrease their narcotic requirement.[8]

Is age a factor in determining the success of sperm retrieval by microTESE? Reifsnyder and associates reported successful sperm retrieval in 62% of men aged 41 to 78 years with clinical pregnancy and live birth rates of 39.8% and 47.1%, respectively.[9] This study suggests that, as long as sperm can be retrieved from a man's testes regardless of his age, the true determinant of a successful pregnancy with intravenous fertilization (IVF) is the female partner's biological clock.

Klinefelter Syndrome

In another cutting edge form of treatment from Mehta and colleagues, nine adolescent boys with Klinefelter syndrome and azoospermia underwent microTESE in order to cryopreserve sperm for possible fertility later in life. The average age of these adolescents was 15.6 years and all had been on exogenous testosterone and daily anastrazole for 1 to 5 years previously. Even though they were on exogenous testosterone, sperm was retrieved by microTESE in seven of the nine boys. Another interesting but unexplained observation in this group of patients was that, with exogenous testosterone treatment together with anastrazole, the LH and FSH levels went from 9.4 and 20.4, to 16 and 35.4, respectively, rather than being suppressed by the testosterone treatment. As Mehta and colleagues stated, this preemptive treatment to retrieve and cryopreserve sperm in this young population of patients with Klinefelter syndrome is truly controversial particularly when the same group reports about their nonadolescent Klinefelter patients (ie, those aged $>$ 40 years).[10] This was shown by Reifsnyder and associates where they reported a 40% sperm retrieval rate in patients with Klinefelter syndrome aged $>$ 40 years,[9] which is somewhat discordant from the data from Japanese investigators Kanto and colleagues, who found that, after age 37, the retrieval rate in their patients with Klinefelter syndrome dropped from 47% to 11%.[11] The determination of whether preemptive sperm retrieval and cryopreservation of the retrieved sperm in these patients with Klinefelter syndrome will become an accepted form of therapy will depend on the ultimate outcome once these sperm are thawed and then used for IVF.

Do frozen sperm initially obtained from a testicular sperm extraction procedure in men with NOA and then thawed have the same fertility potential as fresh sperm obtained from these same men with NOA? Ohlander and coauthors suggested there is no difference. In their review and analysis of 11 robust studies, pregnancy rates were not statistically different between the use of fresh and frozen thawed sperm in NOA couples (28.7% vs 26.4%).[12]

DNA Damage

One conundrum that fertility specialists face is what to do with a male patient who has sufficient sperm for fertilization with IVF and intracytoplasmic sperm injection but who has been previously unable to achieve a pregnancy with the ejaculated sperm. Some insight to this dilemma can be gleaned from the study of Mehta and associates.[13] In this report, the authors compared apoptosis of the ejaculated sperm with that obtained by testicular sperm extraction and found that the testicular sperm had significantly less apoptosis than the ejaculated sperm with the potential to possibly improve fertilization rates.[13] Although controversial and not proven by any level of evidence, this suggests that consideration of using testicular sperm over ejaculated sperm in such a setting may be warranted.

Varicocele

Is it worth fixing a varicocele in a patient who is azoospermic? There are divergent views about this topic in the literature but the presentation of Salem and colleagues from Egypt suggests that this can be determined by a testis biopsy.[14] If the biopsy shows focal spermatogenesis or maturation arrest at the spermatid stage, there is a high likelihood of return of sperm to the ejaculate, whereas if the testis biopsy shows Sertoli-cell-only or maturation arrest at the spermatocyte stage, the prognosis is poor for sperm to return to the ejaculate. FSH, the usual metric we rely on to determine the presence of spermatogenesis, was not predictive of success with the procedure. Again, although this study demonstrated that this surgical procedure can improve spermatogenesis, the evidence that it improves pregnancy rates is still lacking.

Vasectomy Reversal

The majority of men who have had a vasectomy have had proven fertility with a particular female partner. However, the majority of those who then seek a reversal usually have a different female partner whose fertility potential is usually unknown. Could it be that the fertilization rates reported in the literature in men who have had vasectomy reversals are affected by this variable (ie, a different partner)? To glean insight into this, Ostrowski and associates reported that, in 524 such patients, the clinical pregnancy

and live birth rate rates were 83% and 75%, respectively, in these couples.[15] Although the patients and their partners were older (aged 38.9 and 33.2 years vs 35.6 and 30.6 years, respectively), the obstructive interval was 5.6 years in the select group versus 9.2 years for the overall group, suggesting that the difference in the interval rate may also play a role in success rate improvement.

Cancer

Banking sperm prior to cancer treatments has been and remains a priority of oncologists and urologists. However, if sperm banking is not done before orchiectomy, is all hope lost? Teloken and colleagues reviewed 36 patients undergoing orchiectomy for testis cancer who were azoospermic at the time of their orchiectomy. Approximately 38% (14/36) of these patients who were azoospermic preoperatively had sperm return to their ejaculates postoperatively. Many of the azoospermic patients also underwent a TESE postorchiectomy and 73% of these who did had sperm retrieved.[16] Overall, 80% of these cancer patients were able to cryopreserve by one method or another suggesting that all is not lost if sperm banking is not performed before orchiectomy.

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Pediatric Urology

The AUA and the Society of Pediatric Urology (SPU) launched their first joint annual meeting in 2013 in San Diego. The one-day subspecialty meeting held the day before the full AUA meeting expanded to 3 full days of pediatric urology education. Joint sessions offered a scientific program covering pediatric tumor, trauma, stones, hydronephrosis, hypospadias, varicocele, disorders of sexual differentiation, and dysfunctional voiding and neurogenic bladder reconstruction, as well as urinary tract infection and reflux. Panel discussions on a variety of subjects included proximal hypospadias, bladder neck surgery for neurogenic bladder, fetal urology, and posterior urethral valves, as well as new insights into pediatric stone disease.

Isolated Hypospadias and Exposure to Endocrine Disrupting Chemicals During Pregnancy

The meeting got underway with the presentation of the clinical research papers chosen for the annual SPU award. Kalfa and colleagues from France presented their controlled study on isolated hyposapadias and endocrine disrupting chemicals (EDC) during pregnancy performed in the areas of France with the highest prevalence of hypospadias surgery.[17] This paper won first prize for the clinical research award from the Society of Pediatric Urology. Isolated hypospadias (IH) was identified in 300 of 530 boys. The controls consisted of a group of 230 children without penile anomalies. Direct sequencing of the androgen receptor and 5-α reductase genes was performed to detect mutations that may result in hypospadias. Using a detailed questionnaire, parents' domestic and professional exposures to EDC were determined. They also used a validated job exposure matrix for EDC. Using the zip codes of the locations of the pregnancy, type of surrounding hazards, and distance from the hazards, investigators determined the environmental exposure. They found that the distance between potentially contaminated areas and patients' homes was lower in IH than in controls (mean 1.9 ± 2.4 vs 5.4 ± 14.2 km; $P = .04$). They determined that maternal occupational exposure to EDC during pregnancy occurred more frequently in IH cases (39% vs 10%; $P < .001$). This included pesticides (22%), detergents (18.5%), paints (17.5%), cosmetics (12.3%), and industrial chemicals (8.7%). Occupations including hairdresser, maid, laboratory employee, and agricultural worker were more common among the mothers of IH cases than controls (19.3% vs 10.4%; $P = .004$). An increased incidence of IH was found in children whose fathers were working in industrial areas around incinerators and waste regions within a 10-km radius from the place of conception (25% vs 10%; $P < .01$). Agricultural areas did not pose an increased risk for IH. The authors concluded that boys and men with IH who have a genetic defect are linked to maternal exposure to EDC during pregnancy more frequently than control groups in the same geographical locale. They further concluded that parental exposure at around the time of fertilization appeared to be a significant risk factor for the development of IH.

Risk Factors for Febrile Urinary Tract Infections in Children With Antenatal Hydronephrosis

Merrow and colleagues from Hamilton and Toronto, Canada, evaluated risk factors for febrile urinary tract infections (fUTI) in children with antenatal hydronephrosis (AHN).[18] They studied 376 infants from a single center. A prior study showed that antibiotic prophylaxis (AP) reduces UTI rates in patients with high-grade (III-IV) hydronephrosis but did

not examine sex, circumcision status, or vesicoureteral reflux (VUR) status. Using an AHN database, 376 infants who had undergone a voiding cystourethrogram between 2008 and 2012 were evaluated. fUTI was the primary outcome for this study. The majority of infants (74%) were male. One-third of the infants (34%) had high-grade AHN (grade III-IV). Almost two-thirds of the patients (60%) received AP and most of these patients (81%) had high-grade AHN. Reflux was present in 21% of the infants and almost all (96%) were placed on AP. Circumcision status was known for 268 boys (84%), of which 76 of them (28%) were circumcised. Higher rates of fUTI were associated with uncircumcised versus circumcised boys (16%, vs 5%; $P = .01$) and high- versus low-grade AHN (20% vs 10%; $P = .01$). No significant association was found between VUR, AP, and fUTI, most likely due to the high usage of AP in patients with VUR and high-grade ANH. Female infants had a fUTI rate of 16%, which was significantly higher than that of circumcised boys (5%; $P < .01$). The authors concluded that the development of fUTI is significantly linked to high-grade AHN and uncircumcised status. Girls have a similar high risk of fUTI as uncircumcised boys. Further placebo-controlled, randomized clinical trials are needed to examine these questions more definitively.

Antibiotic Resistance Patterns of Outpatient Pediatric UTIs

Hillary Copp, MD, from the University of California San Francisco, presented a State-of-the-Art lecture on antibiotic resistance in pediatric urology.[19] There is increasing resistance to antibiotics that are commonly prescribed in pediatric urology. Resistance has increased due to our prescribing broad-spectrum agents for almost one-third of all pediatric UTIs when most are sensitive to narrow-spectrum antibiotics such as first-generation cephalosporins and nitrofurantoin. Copp noted that ceftriaxone, a third-generation cephalosporin, and trimethoprim/sulfamethoxazole (TMP/SMX) are both overly prescribed. Of concern is that TMP/SMX resistance rates exceed the recommended level for their empiric use in most regions of the United States. The consequences of this are obvious and have led to increased rates of resistance to TMP/SMX used in *Escherichia coli* infections in both boys (23% to 31%) and girls (20% to 23%) between 2004 and 2009.

In addition, the severity of pediatric infections appears to be increasing with more patients hospitalized for treatment of resistant infections in this group. In addition, Copp explained that antibiotic prophylaxis has been commonly used in patients with prenatal hydronephrosis, VUR, and other urologic conditions. A subset of patients on prophylaxis has had an increased rate of resistant UTIs. The use of prophylaxis in these higher-risk groups are the focus of ongoing research and new guidelines.

In conclusion, UTIs, most commonly with *E coli* are here to stay because prevalence rates have remained constant. Copp's group suggests that first-generation cephalosporins and nitrofurantoin are better narrow-spectrum choices than TMP/SMX for empirical treatment of nonfebrile pediatric UTI when considering their low resistance rates. In addition, local antibiograms should be consulted when available for variations in resistance patterns.

[Ellen Shapiro, MD, FACS, FAAP]

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