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A REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY VIEWPOINT ON MALE INFERTILITY KNOWLEDGE GAPS

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ABSTRACT: There has been a tremendous advancement in reproductive science. In other cases, the separation of male and female specialty has allowed researchers to concentrate on specialised areas of study. As a result of the disparity in educational paths taken by male and female reproductive specialists, new information isn't always placed in the context of actual clinical practise. Patients' most important result—the delivery of a healthy newborn—may be overlooked when evaluating therapies based on proxy measures of outcome. Because of the inherent limits of semen analysis for predicting outcomes, medical and surgical therapies that exploit changes in semen characteristics may have only a limited impact on the likelihood of a live birth. In addition to sperm DNA fragmentation testing, several routinely used tests have the potential to explain certain male partners' inability to conceive. However, changes in sperm DNA fragmentation testing are not a suitable endpoint for determining the usefulness of therapies unless well-defined criteria for predicting outcomes in various treatment scenarios are established. For these assays, the most significant constraint is the examination of bulk semen. While sperm can be employed in A.R.T. operations, tests that allow for investigation of its reproductive capacity remain elusive. We are moving toward this goal, but there is still much to understand about how to get there (whether through hyaluronic acid binding, IMSI, or Ramen spectroscopy). Individual sperm testing and collection would improve studies that evaluate the most important outcome for patients & providers—the birth of a healthy baby.

KEYWORDS: Reproductive endocrinology and infertility (REI), Assisted reproductive technologies (ART), Infertility, Male infertility.

INTRODUCTION:

One of the most remarkable aspects of fertility experts' work is that they treat two patients simultaneously. Reproductive urologists & reproductive endocrinologists tend to treat male and female patients separately because of the training paradigms in place (RE). Reproductive medicine has become increasingly specialised, allowing researchers to focus on certain aspects of the discipline, but this has also led to inefficiencies in the study of the reproductive process. RE, on the other hand, has a female-dominated approach to couples. Following assisted reproduction, urologists may have little to no experience with the ensuing steps (such as embryo culture and transfer).

As a result of our teaching system, there is a noticeable gender focus gap in the research on fertility. Many studies (in both male and female patients) have relied on surrogate outcome markers that are more related to the breadth of treatment delivered by the clinician scientists arranging the study rather than studying the entire process. When it comes to men's reproductive health, for example, treatments that improve semen parameters or fertilisation efficiency may signal some improvement, but the present literature often fails to determine if a meaningful rise happened in the likelihood of delivering a healthy kid.

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Endpoints that were once regarded crucial in the field of reproductive medicine are now rendered obsolete by the rapid advancement of knowledge in this field. It's imperative that the goals of every diagnostic test and treatment strategy be reevaluated in light of today's therapeutic paradigms. When it comes to fertility treatments, a medication that increases the number of embryos ready for transfer on day three appears to be a huge advantage. However, in an era with blastocyst culture, preimplantation genetic testing, & single embryo transfer, this outcome may be less relevant. It is time to reassess assisted reproductive technology's focus on enhancing the efficiency of treatment so that greater selection chances are available. This means that instead of focusing simply on surrogate outcomes such as increasing sperm output, the most important concerns in reproductive medicine are centred around selecting the one embryo that is most likely to result in the live birth of a healthy, singleton baby.

There have been numerous significant advances in the study of male fertility, which will be discussed in this article. In addition, the system will seek to identify places where information is lacking. Rather than criticising male reproductive research, this remark serves as a guide for the RE's perspective on treatment alternatives for males. Research findings should be examined often to ensure that they stay relevant when treatment paradigms change throughout time, according to one view of this process. As a result, we hope that this new approach will lead to a new age of cooperation that will benefit our patients and help them realise their goals in raising healthy families.

CURRENT RESEARCH IMPLICATIONS AND CHANGES IN FERTILITY THERAPY PARADIGMS:

Since the introduction of the first reproductive medicine training programmes in the mid-20th century, the field has undergone a substantial shift in focus. Initially, the majority of programmes in reproductive endocrinology research and instruction arose within internal medical departments [1]. The hypothalamic-pituitary-gonad axis was commonly treated by the same doctors for both men and women at this time. There was less distinction between male and female patients in research and clinical care when therapy options were restricted.

[2] In the 1970s, the American Board of Obstetrics and Gynecology (ABOG) recognised the specialisation of REI, and fellowship programmes for gynaecologists were launched. At Johns Hopkins (and later Eastern Virginia Medical School), at the University of California, at Yale, and at Howard and Georgeanna Seeger Jones's (and later Robert Jaffe and Samuel Yen's) (and later Eastern Virginia Medical School's) (and Leon Speroff's) (and later Eastern Virginia Medical School's) (and later Oregon Health Sciences University). As obstetricians and gynaecologists, these luminaries paved the way for the field of REI to become more focused on women's health.

The early days of REI training maintained a focus on reproductive endocrinology because it emerged from within internal medicine. Hormonal assays and the physiologic basis for illnesses including premature puberty, primary amenorrhea, and ambiguous genitalia took a lot of effort to develop and test. Advanced surgical training in microsurgery as well as the development of laparoscopy were added to this foundation. Endocrinopathies connected to reproduction and surgical operations on female patients, such as tubal re-anastomosis or fimbrioplasty, were thus relying on RE to understand the physiologic basis for endocrinopathies [3].

Reproductive medicine's focus shifted dramatically with the introduction of in vitro fertilisation (IVF) [4]. From hormone tests and surgery to cell culture and gamete biology, the

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focus of research and clinical care has changed dramatically. Both male and female gametes were investigated to better understand the physiological needs of fertilisation and preimplantation embryo development, bringing the treatment of male and female patients closer together.

In embryo cultivation, doctors have made only a small number of the most significant achievements. Indeed, classically trained embryologists from the animal science realm have had a significant impact on human IVF [5]. REs as well as male reproductive specialists were involved in many treatment paradigms that improved clinical IVF success, including such gonadotropin stimulation protocols, but their clinical training rarely interpreted into major contributions to clinical embryology, including such extended embryo culture or cryobiology. They were. The basic sciences were responsible for these developments. As a result, assisted reproductive technology (ART) laboratories were gradually removed from the clinical world. Male infertility treatment options improved as ART progressed, and urology departments began to focus on male fertility research. Male and female partners have traditionally been treated by the same doctor up until this time. For the most part, this was a RE. After the first successful surgical sperm retrieval reports, things began to change. Treatment for couples with restricted options prior to this innovation and the availability of micromanipulation options has been revolutionised [6,7]. As a result of the surgical nature of these high-profile discoveries in the treatment of male infertility, urologists came to dominate the field. Male reproductive and sexual function research and microsurgical methods for sperm retrieval have grown as a result of training programmes that support study in these areas.

As the study of reproductive biology and the practise of fertility medicine becomes more specialised, there is a higher risk of losing a holistic view of the couple under treatment. Reproductive endocrinologists, for example, tend to prioritise the number of oocytes that can be harvested from an artificial insemination cycle over the quality of the embryos that can be implanted in the uterus. The contemporary literature on male infertility also focuses on quantifiable outcomes, such as the success rate of sperm retrieval following surgery.

In light of this contemporary reality, there has been significant dispute about whether integrated training programmes in male and female infertility, whereby one physician assumes the majority of care for a couple attempting pregnancy, are best. There are many ways to address this issue, but a simple one is to strengthen collaboration between REs & male reproductive experts to ensure that the most important endpoints are being studied. [9] A university medical centre with access to both male and female reproductive specialists is the most obvious place for this kind of collaboration to take place. The REI & urology departments in many centres have already achieved significant progress in enhancing patient care through collaborative efforts. Male fertility specialists have also recently been employed by several of the country's leading private fertility clinics. This method enables urologists and REIs to work together more closely on research projects by centralising all of a couple's care in a single location.

SEMEN STUDY:

The most extensively used test for evaluating male fertility is the semen analysis. These glands' functions and the efficacy of their spermatogenesis are explained in detail. However, the conventional semen analysis's usefulness in assisting clinicians in counselling patients about their chances of becoming pregnant has been hotly debated [11]. Uncertainty surrounds the definition of the features of semen that distinguish between fertile and infertile men. Individual criteria, such as morphology, have not been found to reliably correspond with

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pregnancy rates. Because of these and other limitations, semen analysis remains an ineffective technique for counselling.

For starters, a man's fertility can't be accurately predicted based on just one or two ejaculates because of the wide range of factors that can be found among them. Within-subject variation in sperm concentration was shown to be as high as 26.8% over a 10-week period in one elegant investigation. For this reason, the World Health Organization has urged men to get at least three separate semen analyses to get a true picture of their fertility. This is critical, given that males with previously abnormal specimens tend to have increased sperm concentration and motility during the second test. In most cases, these individuals are people who have been selected for research investigations because of their apparent low fertility. Studies that use improvements in semen parameters as a primary outcome must account for this heterogeneity.

Furthermore, there is evidence of considerable inter- and intra-observer variability in parameter reporting when employing the semen analysis in a research setting. Sperm morphology, vitality, concentration, and total motile sperm count were all found to vary by 70 percent, 40 percent, 34 percent, and 20 percent, respectively, among laboratories. Even in laboratories that adhere to rigorous quality control procedures, there are still variations in the results of semen analysis. A discrepancy in semen analysis results from one lab to another, independent of quality control accreditation, may not be indicative of a clinical difference.

Furthermore, it has been shown that morphological testing has little to no predictive value. This data point is not indicative of pregnancy rates following IUI or IVF, even though showing technician skill in morphologic testing is a major goal in andrology labs. Even if an effective quality control method ensures that results are consistent among and between technicians, a test that does not predict pregnancy has very little usefulness.

When it comes to ART, the greatest drawback to semen analysis may be its inability to examine sperm function. As many as 30% of men in infertile couples do not show any abnormalities in their semen during testing. Despite normal parameters, many of these guys end up in IVF and still show poor fertilisation or limited embryo development, which suggests reduced sperm function. In light of this, a thorough examination of the male reproductive system is critical. In order to investigate sperm cell membrane integrity, acrosome function (ARIC), zone binding (hemizona assay), interaction with oolemma (hamster zona-free ovum test), or autoimmune, numerous adjunct tests of sperm motility have also been created (sperm antibody testing). But the predictive usefulness of each test is either extremely limited or poorly defined. IVF pregnancy rates, for example, do not correlate well with sperm antibodies. For infertile couples, it's still not apparent where to position supplementary testing of sperm function.

Semen parameters alone before and after an intervention provide only little information about the most crucial issue to both patient and clinician—the delivery of a healthy newborn. As an example, investigations on the male thalamic axis in oligozoospermic males should not only enhance semen analytical parameters but also demonstrate an increase in the number of oocytes delivered. The most important study topic is whether or not these individuals can avoid more invasive, expensive treatment (IVF) by attaining satisfactory pregnancy rates as a result of their increased spermatogenic function. Contrarily, research should not only examine improvements in semen characteristics but also ascertain whether these improvements enhance delivery rates when a couple uses IVF and ICSI for any other reason (when just one sperm is required per egg). There are two ways in which the treatment strategy for each couple helps define the research topics that should be asked:

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TESTS FOR FRAGMENTATION OF SPERM DNA:

Sperm chromatin integrity assays are the most commonly used and extensively studied supplementary diagnostics for male infertility [12]. Infertile men are more likely than fertile to have a high level of sperm DNA damage [13]. SDF (sperm DNA fragmentation) is connected with repeated pregnancy loss and may contribute to increased reproductive dysfunction according to the ASRM Practice Committee. However, there are still many unanswered questions with DNA fragmentation testing.

Since there is no standard for defining aberrant DNA fragmentation, the current literature is severely limited by this issue. Samples with more than 7 percent, 15 percent, or 30 percent fragmentation have been termed "elevated" in different investigations using the same method. The fundamental studies' lack of statistical rigour in setting threshold values has given rise to this contradiction. Additionally, the number of studies has been too small and the level of control for female variables has not been adequate to produce reasonable estimates of sensitivity and specificity for delivery at each possible abnormality. There are numerous commercially available sperm DNA fragmentation assays, however little information is available on whether these assays correlate with each other in terms of sperm DNA fragmentation levels [14]. In order to identify the optimal applicant to whom a test might provide novel and therapeutically useful information, it is challenging for any biomarker of infertility to assess repeatability and set unambiguous thresholds for abnormality. Sperm DNA fragmentation has not yet achieved this goal.

Even while existing research suggests that high levels of DNA fragmentation are related with a decrease in natural fertility, knowledge about how these test results effect the likelihood of success in various treatment options is far more restricted. There are mixed results from studies looking at the effect of SDF on the success rate of IUI cycles. SDF levels were found to be linked with pregnancy rates in a prospective cohort research that included IUI and controlled ovarian hyperstimulation (COH) cycles. There was no association between SDF levels and pregnancy rates in 100 cycles studied by another research team.

When traditional insemination is utilised, there is more evidence that high SDF decreases IVF success (median PPV estimated at various thresholds for IVF failure of 77%). While this meta-analysis included a large number of studies, many of them tiny and lacking in control groups, it's not clear how reliable this information is. Studies with ICSI have yielded similar outcomes. Even though high levels of SDF are associated with lower conception rates, a recent meta-analysis found that ICSI use outweighs this effect (at various thresholds).

Because of this, both female and male experts are today confronted with the difficulty of when to request SDF testing and the counselling dilemmas of how to interpret the results, even though the existing data show a biological link between SDF levels and diminished fertility. A much more needs to be done.

VARICOCELE:

It has been shown in large descriptive studies that men who seek assessment for their fertility are more likely to present with varicoceles than those who have been declared fertile. Varicoceles' effect on a couple's ability to become pregnant has been difficult to pin down. Semen parameters may be abnormal in males with varicoceles. Couples with abnormal male semen parameters and normal female work-ups may benefit from varicocelectomy treatment

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of a varicocele. This is because treatment of a varicocele in these couples, particularly young ones with the luxury of extra time, appears to improve spontaneous pregnancy success rates.

Asymptomatic varicocele in a couple planning to undergo IVF/ICSI raises some questions about the effectiveness of treatment. In most trials evaluating varicocele treatment, improvement in semen parameters has been the only measure of success. Sperm motility improved by 11% and concentration rose by an average of 12 million/mL in one research. Even while improved sperm parameters signal a return to normal spermatogenic function, the limits of semen analysis are well-documented as shown in the previous section. IVF/ICSI success rates have been proven to be unaffected by semen parameters. In cases when IVF/ICSI is already planned for female indications, the ASRM Practice Committee recommends against varicocelectomy. According to current research, men with oligozoospermia and varicoceles should have their varicoceles removed prior to IVF in order to increase their live birth rates. Varicocelectomy has been shown to enhance the possibility of the ejaculate containing sperm following repair in males with non-obstructive azoospermia, while reported success rates vary greatly. As a result, IVF or ICSI can be performed without sperm retrieval surgery thanks to a varicocelectomy. Even after varicocelectomy, many men still need surgical sperm retrieval, raising doubts about the therapeutic and financial benefits of varicocelectomy for these individuals. Varicocele surgery may be unnecessary for certain men because of the potential that enough sperm will return to the ejaculate to justify IUI efforts. More information, however, is unquestionably required [15].

There is a need for greater research into the characteristics of male patients who have had varicocele surgery and have shown considerable improvement. This knowledge is critical for couples who are considering a varicocelectomy and subsequent fertility treatments, as it normally takes three to six months for sperm to return to normal following the procedure. Future research is needed to discover this prognostic information, as not all patients have had the luxury of time, depending on the outcome of the female work-up.

IVF/ICSI SPERM SELECTION:

There is a major drawback to current laboratory estimates of male fertility because semen is mainly examined in bulk. One sperm cannot currently be evaluated and isolated for usage according to the results of an analysis because there is no test available that can do so. It's not possible to determine which of a man's sperm have the greatest reproductive potential, even if they show signs of spermatogenic failure (either through semen analysis, DNA fragmentation assay, or sperm functional assays). Patients and doctors alike would greatly benefit from a diagnostic test that could tell them whether or not a sperm is functioning properly without destroying it.

These assays that try to extract the most reproductively competent sperm after washing procedures have limited clinical evidence to support their usage at this time. Morphology evaluation can be done at high magnification (at least 6,000) with IMSI, which helps labs detect tiny anomalies that would otherwise go unnoticed at lower magnification levels. In spite of some promising initial outcomes, the trials' methodological rigour is lacking. IMSI patients had larger oocyte yields and more embryos transferred in four of nine prospective studies that evaluated clinical pregnancy rates as an endpoint, showing that IMSI patients had a better prognosis than ICSI patients. The only study to compare IMSI with ICSI on the basis of live birth outcomes found no differences between the two methods. It's also been debated

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as to whether or not certain IMSI-labeled aberrant morphologic traits (such as the presence of vacuoles) actually indicate normal physiological processes.

HA binding assay is the second most well-researched approach for sperm selection. According to this test, spermiogenesis-induced membrane changes lead to the development of HA-binding sites. Aneuploidy and indicators linked with apoptosis were shown to be less common in HA-bound sperm, according to early studies. Embryos from oocytes injected with HA bound sperm were found to have a higher implantation rate in future clinical trials using ICSI, but the implantation rates in this study were low (10.3 percent control vs. 17.1 percent study group, P0.05). Low implantation rates make it impossible to tell if this improvement can be duplicated in current ART techniques, which normally have greater rates of implantation than those in this trial. Another prospective study on sperm selection for ICSI using HA binding sperm has been halted before it could reach the intended sample size due to lack of funding, but the available data show a trend toward improved clinical pregnancy rates (50.8 percent vs 37.9 percent, P>0.05) and a significant decrease in pregnancy loss (3.3 percent vs 15.1 percent, P=0.02). There are still issues about the relevance of this study's practise patterns, though. On days 2, 3, and 5, the embryos were transplanted in this trial, and a single patient received up to 7 blastocysts. IVF facilities perform primarily blastocyst transfers, with the occasional day 3 transfer, in their present practise. In addition, most clinics limit the number of embryos that can be transferred in a single round to two. However, the facts addressing the selection of sperm that binds to HA are sufficiently encouraging that more research is definitely necessary.

IN ADDITION TO SEMEN ANALYSIS, ADVANCED SPERM DIAGNOSTICS:

Idiopathic male infertility may require more effective tools to uncover the mechanisms at play because of a lack of semen analysis' ability to classify men as fertile or infertile and treatments like endocrine manipulation or surgical correction of varicocele have only shown inconsistent improvement with meaningful outcomes. Sperm epigenetics testing is a potential new approach. In a recent elegant work, sperm DNA methylation was analysed across the entire genome and the top 100 differentially methylated CpG sites were discovered in 127 different samples of sperm [16]. An algorithm developed by the researchers was capable of predicting men's reproductive status with an accuracy rate of 99 percent. Men's reproductive health professionals may find it more beneficial to use more precise instruments like this one than the ones they now have at their disposal.

If you want to get a sense of how many different kinds of DNA methylation patterns you'll find in your ejaculate, you'll need an epigenetic profile. Even Nevertheless, it has been shown that the level of methylation differs amongst individual sperm in the same ejaculate. Since each diagnostic assay would benefit greatly from the capacity to extract sperm with the appropriate molecular traits, this would allow for the selection of sperm with enhanced reproductive capabilities.

SPERM SORTING:

If sperm sorting procedures were accessible, they would improve the value of all present diagnostics that use a sperm pool to produce a profile of a patient's reproductive competence. Spermatogonial stem cells appear to be affected differently by male infertility disorders [17][18]. The number of de novo mutations varies among sperm, according to the theory of the selfish spermatogonial stem cell. Even within a single ejaculate, the epigenetic alterations differ. Men who are less fertile, even if they have higher levels of damaged sperm, nonetheless have plenty of reproductively competent sperm on their hands. Normal

embryogenesis and better pregnancy outcomes in IVF cycles, whether using ICSI or not, are quite likely if these can be separated and used clinically.

Developing new technology for separating sperm is a hot topic in the scientific community. Many microfluidics devices have been reported to sort sperm based on a variety of different parameters. The female reproductive tract's physiology plays a role in several of these technologies, such chemoattractant or thermotaxis microfluidics. Single sperm can be interrogated for chemical features using other instruments, such as Raman spectroscopy—one especially fascinating technology is the use of Raman spectroscopy.

The combination of Raman spectroscopy and microfluidics devices, while still requiring more study, could allow for the temporary trapping of individual sperm for molecular analysis and the shunting of desirable sperm to various channels for therapeutic usage. Microfluidics may allow sophisticated diagnostics to be employed in conjunction with sperm selection in the future. The use of microfluidics may be particularly beneficial when sperm sorting is required (and time-consuming), as in the case of a search after micro-TESE. Urologists, REs and andrologists, molecular biologists and engineers would all be involved in the development of a useful instrument such as this. In the 21st century, team-based techniques are the norm in science, and they are essential for a future in which therapeutic outcomes improve.

CONCLUSIONS:

Infertility patients have benefited greatly from new discoveries and treatment choices thanks to increased specialisation and division between male and female subspecialists. As the success and safety of our treatments continue to improve, we may be happy of the progress we have made as a medical specialty. Sequestration, on the other hand, has the potential to obscure the interconnectedness of care. Keeping a broad view of infertility therapy has become much more challenging, and collaborating with colleagues requires more work now that we are often apart.

Only a few of the subjects that could benefit from more collaboration are discussed in this review. As the ground beneath us continues to shift, it would be beneficial for our field to do periodic reviews to see whether or not the treatment we presume is evidence-based should still be advised. Even though male and female subspecialists share the ultimate goal of improving the rate of live birth for couples with infertility, both laboratory scientists and clinicians need to keep this in mind as we continue to evaluate our current treatment paradigms and search for new methods of diagnosing and treating these patients.

REFERENCES:

1. Gambone JC, Segars JH, Cedars M, et al. Fellowhship training and board certification in reproductive endocrinology and infertility. *FertilSteril* 2015; 104:3-7
2. Barnhart KT, DeCherney AH. Are reproductive endocrinologists still gynecologists. *FertilSteril* 2015; 104:24-5.
3. Palermo G, Joris H, Devroey P, et al. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992; 340:17-8.
4. de Ziegler D, de Ziegler N, Sean S, et al. Training in reproductive endocrinology and infertility and assisted reproductive technologies: options and worldwide needs. *FertilSteril* 2015; 104:16-23

5. Poland ML, Moghissi KS, Giblin PT, et al. Variation of semen measures within normal men. *FertilSteril* 1985; 44:396-400.
6. Alvarez C, Castilla JA, Martinez L, et al. Biological variation of seminal parameters in healthy subjects. *Hum Reprod* 2003; 18:2082-8.
7. Baker HW, Kovacs GT. Spontaneous improvement in semen quality: regression towards the mean. *Int J Androl* 1985; 8:421-6.
8. Barroso G, Mercan R, Ozgur K, et al. Intra- and inter-laboratory variability in the assessment of sperm morphology by strict criteria: impact of semen preparation, staining techniques and manual versus computerized analysis. *Hum Reprod* 1999; 14:2036-40
9. Cooper TG, Björndahl L, Vreeburg J, et al. Semen analysis and external quality control schemes for semen analysis need global standardization. *Int J Androl* 2002; 25:306-11.
10. Zini A, Fahmy M, Belzile E, et al. Antisperm antibodies are not associated with pregnancy rates after IVF and ICSI: systematic review and meta-analysis. Hum Reprod2011; 26:1288-95.
11. Leushuis E, van der Steeg JW, Steures P, et al. Immunoglobulin G antisperm antibodies and prediction of spontaneous pregnancy. FertilSteril2009; 92:1659-65
12. Leifke E, Nieschlag E. Male infertility treatment in the light of evidence-based medicine. Andrologia1996; 28:23-30.
13. Mehta A, Bolyakov A, Schlegel PN, et al. Higher pregnancy rates using testicular sperm in men with severe oligospermia. FertilSteril2015; 104:1382
14. Greco E, Scarselli F, Iacobelli M, et al. Efficient treatment of infertility due to sperm DNA damage by ICSI with testicular spermatozoa. Hum Reprod2005; 20:226-30.
15. Muriel L, Meseguer M, Fernandez JL, et al. Value of the sperm chromatin dispersion test in predicting pregnancy outcome in intrauterine insemination: a blind prospective study. Hum Reprod2006; 21:738-44.
16. Zini A. Are sperm chromatin and DNA defects relevant in the clinic? Syst Biol Reprod Med 2011; 57:78-85.
17. Nagler HM, Luntz RK, Martinis FG. Varicocele. In: Lipshultz LI, Howards SS. editors. Infertility in the male. St. Louis, MO: Mosby Year Book; 1997:336-59.
18. Abdel-Meguid TA, Al-Sayyad A, Tayib A, et al. Does varicocele repair improve male infertility? An evidence-based perspective from a randomized, controlled trial. EurUrol2011; 59:455-61