Clinic Rev Allerg Immunol (2012) 42:256–263
DOI 10.1007/s12016-011-8281-z

Cutting-Edge Issues in Autoimmune Orchitis

Clovis A. Silva · Marcello Cocuzza · Eduardo F. Borba · Eloísa Bonfá

Published online: 13 August 2011

Abstract Autoimmune orchitis is a relevant cause of decreased fecundity in males, and it is defined as a direct aggression to the testis with the concomitant presence of anti-sperm antibodies (ASA). The presence of these specific antibodies has been observed in approximately 5–12% of infertile male partners. Primary autoimmune orchitis is defined by isolated infertility with ASA but without evidence of a systemic disease. Secondary causes of orchitis and/or testicular vasculitis are uniformly associated with autoimmune diseases, mainly in primary vasculitis such as polyarteritis nodosa, Behçet's disease, and Henoch–Schönlein purpura. The overall frequencies of acute orchitis and ASA in rheumatic diseases are 2–31% and 0–50%, respectively. The pathogenesis of primary/secondary autoimmune orchitis is not completely understood but probably involves the access of immune cells to the testicular microenvironment due to inflammation, infection or trauma, leading to apoptosis of spermatocytes and spermatids. Glucocorticoids and immunosuppressive drugs are indicated in autoimmune orchitis-associated active systemic autoimmune diseases. However, there are no standardized treatment options, and the real significance of ASA in infertile men is still controversial. Assisted reproductive technologies such as intrauterine insemination, in vitro fertilization, and intracytoplasmic sperm injection (ICSI) are therapeutic options for male infertility associated with these autoantibodies. ICSI is considered to be the best choice for patients with severe sperm autoimmunity, particularly in males with low semen counts or motility.

Keywords Autoimmune orchitis · Testicle · Antisperm antibodies · Fertility · Orchitis

C. A. Silva
Pediatric Rheumatology Unit, Department of Pediatric,
University of Sao Paulo,
Sao Paulo, Brazil

C. A. Silva (✉) · E. F. Borba · E. Bonfá
Division of Rheumatology, University of Sao Paulo,
Av. Dr. Arnaldo 455, office 3133,
01246-903 São Paulo, Brazil
e-mail: clovis.silva@icr.usp.br

M. Cocuzza
Department of Urology, University of Sao Paulo,
Sao Paulo, Brazil

Introduction

Spermatogenesis and steroidogenesis are the two major functions of the testis [1]. Testicles are mainly composed by seminiferous tubules that have germ cells (stem cells, spermatogonia, spermatocytes, and sperm) and Sertoli cells that produce inhibin B [2]. They also have interstitial region which is composed by Leydig cells that produce testosterone [3]. Sperm production in the testicles usually begins at puberty, between 12 and 13 years old, and thereafter, spermatozoa are constantly produced [1, 2].

Testicular dysfunction and infertility can be multifactorial, particularly in patients with chronic illness [2, 4–8]. Impaired health status such as malnutrition [6], obesity, alcohol, tobacco, or illicit drug use [9] may reduce fertility [10, 11]. Furthermore, hypothalamic–pituitary–gonad axis dysfunction [12–15], inflammatory disease activity or chronic renal failure [1, 2, 16], immunosuppressive drugs [17–20], genetic abnormalities (Klinefelter's syndrome and *Y*-chromosomal microdelections) [21], and the presence of anti-sperm antibodies (ASA) can induce impairment in male reproductive function [1, 2, 4–6, 8, 22–24].

Orchitis is defined as an acute symptomatic disease following a local or systemic infection [25]. The subacute or chronic asymptomatic inflammation of the testis, including those of non-infectious disease etiologies, is hardly ever diagnosed and for this reason, often unnoticed. Additionally, testis inflammatory diseases may also encompass the epididymis and vice versa (epididymo-orchitis) [23].

Epididymo-orchitis may be classified according to its cause such as infections (bacterial/viral) or traumatic events (testicular torsion). The most common trigger of viral orchitis is mumps [26]. Orchitis may also be associated with accessory gland infection, such as prostatitis or sexually transmitted diseases, particularly *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections, and rarely enterobacteriae [27].

Definition and Classification of Autoimmune Orchitis

Autoimmune orchitis is defined as an autoimmune aggression to testis [25] with the presence of specific testis autoantibodies and is a cause of decreased fertility in males [28] and females [29]. According to its main cause, this entity may be classified in:

1. Primary autoimmune orchitis-isolated infertility in presence of autoantibodies (ASA or antibodies to the basement membrane or the seminiferous tubules) [25] and without evidence of systemic disease.
2. Secondary autoimmune orchitis–orchitis and/or testicular vasculitis associated with a systemic autoimmune disease [25].

Epidemiology

The presence of ASA in primary autoimmune orchitis has been observed in the serum and/or in the seminal plasma or attached to the surface of spermatozoa in approximately 5–12% of infertile male partners [26, 30, 31], whereas autoimmune response against the developing germ cells of human testis has not been studied extensively [25]. These autoantibodies may also be detected in follicular fluid and cervical mucus in female partner. However, only the antibodies bound to spermatozoa are relevant for fertility [26].

These ASA were also described in men with unilateral and bilateral obstruction of vas deferens [28] and after vasectomy [30], torsion or testicular injury [32], especially in infertile patients with oligozoospermia (reduction of sperm concentration) [31, 33]. The presence of these antibodies have also been documented in other conditions including sexually transmitted diseases, varicocele, mumps orchitis, and spinal cord injury [28].

On the other hand, in secondary orchitis due to systemic autoimmune diseases, a prevalence of ASA in 7% of males with chronic rheumatic diseases was demonstrated in a recent study, even in the absence of other contributing factors to develop these autoantibodies (such as vasectomy, testicular trauma, etc.) [34].

Interestingly, ASA antibodies were reported in approximately 13–50% of systemic lupus erythematosus (SLE) patients, but a clear association with infertility was not identified [22, 34, 35]. Reichlin et al. reported IgG antisperm antibodies in almost half of 24 SLE patients, which were related to anti-DNA titers and disease activity, suggesting the possibility of an antibody-mediated lesion. Recently, our group confirmed an overall ASA frequency of 40% in 35 male adolescents and adults with SLE [22]. However, in this global evaluation of gonadal function, these antibodies were not associated with sperm abnormalities severity, reduction of testicular volume, hormone alterations, and cyclophosphamide therapy [22]. Additionally, epididymo-orchitis was a rare manifestation of lupus [16, 36, 37] and one case of lupus/scleroderma overlap syndrome [38].

Testicular involvement in connective tissue diseases is typically caused by medium-vessel vasculitis as described in polyarteritis nodosa (PAN) [39]. Orchitis or testicular tenderness occurs in 2–18% of patients with this disease [39–43], although autopsy studies identified frequencies as high as 93% [39]. In contrast, isolated form of PAN with testicular involvement was rarely reported [40].

Acute clinical epididymo-orchitis was also observed in 4–31% Behçet's disease [39]. This manifestation could be recurrent in 12% of patients with this vasculitis and other associated symptoms include oral ulcers, uveitis, arthritis, and penile ulcer [44]. Orchitis was evidenced in 7–21% of Henoch–Schönlein purpura [39, 45, 46]. There were two reported cases of this urologic alteration in relapsing polychondritis [39] and two cases in rheumatoid arthritis [39, 41]. Scrotum and testicular calcinosis in juvenile dermatomyositis was described in two pre-pubertal patients of our idiopathic inflammatory myopathies population [7]. The frequencies of orchitis and ASA in autoimmune rheumatologic diseases are shown in Table 1.

Immunopathogenesis

The immunopathogenesis of autoimmune orchitis is shown in Fig. 1. Testis has a unique immune condition because it is able to tolerate autoantigens expressed in germ cells [26, 47] after puberty when immunocompetence is established [48]. It is believed that the underlying pathogenic mecha-

Table 1 Orchitis and anti-sperm antibodies in autoimmune rheumatic diseases

Autoimmune disease	Orchitis	ASA	Reference
Primary vasculitis	2–31%	25%	[34, 39]
Behçet's disease	4–31%	0–25%	[34, 39, 44]
Henoch–Schönlein purpura	7–21%	ND	[39, 45, 46]
Polyarteritis Nodosa	2–18%	ND	[39–43]
Systemic lupus erythematosus	3 cases	13–50%	[5, 22, 34, 36–39]
Idiopathic inflammatory myopathy	2 cases	0–20%	[6–8]
Relapsing polycondritis	2 cases	ND	[39]
Rheumatoid arthritis	2 cases	25%	[39, 42, 57]
Systemic scleroderma	1 case	0%	[34, 38, 39]

ASA Anti-sperm antibodies, *ND* not described

nism involved in the testicular autoimmune disease is a T-cell response to antigens or microorganisms that have permeated the testis barrier [25]. Indeed, the prevention of this autoimmune disease involves the blood–testis barrier, a structure that protects the access of germ cells antigens to the immune cells and antibodies [48].

Studies on experimental autoimmune orchitis (EAO) have helped to partially elucidate not only organ-specific autoimmunity [49, 50], but also the systemic and local regulation that normally prevents disease in the testis [26]. The most likely mechanism for blood–testis barrier breakdown during inflammation is cytokines. An increase in tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) levels may downregulate occluding expression in Sertoli cells with a consequent disassembly of its tight junctions [51]. Macrophages, endothelial, and Leydig cells secrete chemokines (MIP-1 alfa, MIP-1) that bring about the outflow of immune cells to the testicles

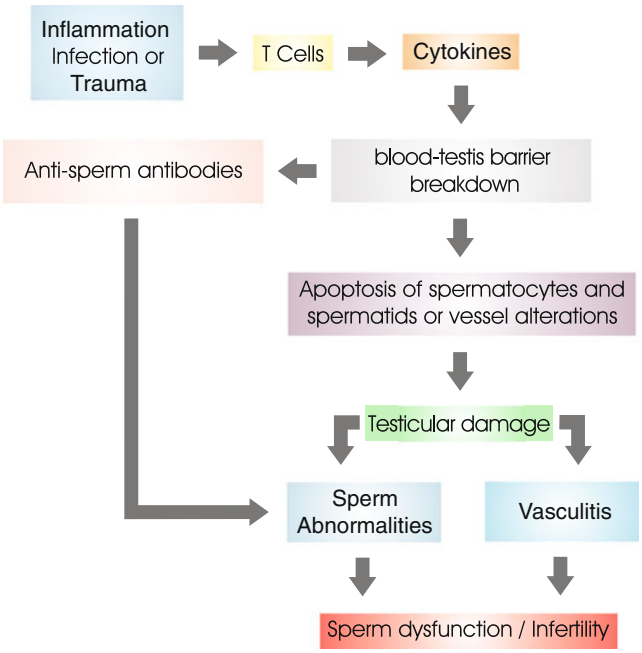

Fig. 1 Immunopathogenesis of autoimmune orchitis

[50]. Dendritic cells with a mature immunogenic state determine immune response against spermatic antigens in the testis induced by EAO [52].

Moreover, immune cells secrete other pro-inflammatory cytokines such as IFN-γ, IL-1, IL-6 [48, 51], IL-12, IL-17, and IL-23, which modify the normal testicular environment [52]. These mechanisms induce inflammation with increased numbers of germ cells expressing TNFR1, IL-6R [52], and Fas/Fas-ligand system leading apoptosis of spermatocytes and spermatids [53, 54]. In addition, the mast cells release proteases in testicular intersticium and peritubular area and probably contribute to fibrosis [50]. Recent data have also demonstrated that activation of toll-like receptors identified in mouse Sertoli cells increases these pro-inflammatory cytokines [55].

The histopathology progression of orchitis can also be learned from studies in EAO [56] and in the early stages is characterized by peritubular and/or interstitial mixed cellular infiltrates [25]. Subsequently, there is mononuclear cells infiltration into the interstitium and sloughing of germinal cells begins to occur, with granuloma formation, necrosis, and complete absence of spermatogenesis [49]. EAO is a T-cell-mediated disease in which the inflammatory CD4 (Th1) T-cell mechanism is the critical pathway that targets the spermatogenic germ cells for autoimmune attack [49]. In spite of the knowledge of local, genetic, and immunological factors, the underlying mechanism of EAO is still not completely understood [25].

In human autoimmune orchitis, the typical pathological feature in testicles resembles those observed in EAO and is characterized by a severe vasculitis leading to inflammation and infarction of reproductive system. Acute and chronic inflammation [16] with lymphoplasmocytic infiltrate [42], fibrinoid necrosis of the vessels [40, 42], and seminiferous tubules [57], and periarteritis in varying amounts are present [39]. Infarction was observed in testicular lesions of PAN [42] and in rheumatoid arthritis [39].

Semen alterations are the direct consequence of this process, and there are few studies regarding the possible triggers at molecular levels. In this regard, there are some

evidence suggesting a possible role of reactive oxygen species (ROS) in male infertility [58]. Excessive generation of ROS in the reproductive tract not only affects the fluidity of the sperm plasma membrane, but also the integrity of DNA in the sperm nucleus [59]. In addition, the extent of sperm DNA damage has been reported to be closely associated with impaired sperm function as well as male infertility [60]. Moreover, the degree of DNA damage seems to correlate with various fertility indices including fertilization rate, embryo cleavage rate, implantation rate, pregnancy rate, and live birth rate [61–63].

Importantly, the most consistent evidence for autoimmune orchitis is the presence of ASA [26]. They can be found in seminal fluid and plasma in men, and also in cervical mucus, oviductal fluid, or follicular fluid in women [25]. The presence of ASA can lead to the immobilization and/or agglutination of spermatozoa, which may significantly impair sperm motility affecting acrosome reaction, cervical mucus penetration, zona pellucida binding [26] and sperm–egg interaction [31]. Also ASA can prevent implantation and/or arrest embryo development. Interestingly, only ASA bound to sperm surface and acrosomal antigens are relevant for fertility [28], whereas the finding of iso-ASA in men and women's sera do not appear to have clinical implications [64]. These later antigens include PH-20, PH-30, FA-1, sperm agglutination antigen-1 (SAGA-1), and SP-10 [28]. In addition, males with ASA had more often HLA DR6 and DQ7 compared to controls [65].

Clinical Manifestations

The usual clinical manifestation of the primary autoimmune orchitis is isolated infertility [25] since most cases of orchitis is asymptomatic. The signs and symptoms of orchitis, when present, are often difficult to distinguish from those of other acute scrotal processes, mainly acute testicular torsion [25]. Generally, the scrotum is inflamed and swollen, and there may be localized testicular pain during palpation, which may be associate or not with fever. Mild thickness of the peritesticular membranes may be also evidenced in some patients [23].

An immunologic basis for some cases of infertility has been identified in a significant number of infertile men, suggesting that ASA may have a harmful effect in fertilization [66]. The term infertility is used to describe the situation where a couple does not succeed in achieving a spontaneous pregnancy in spite of attempting to conceive during at least 1 year of unprotected intercourse [67]. Immunologic infertility is characterized by the presence of antibodies against spermatozoa in the serum and/or in the seminal plasma or on the sperm surface. Secondary autoimmune orchitis is rare and is mainly associated with primary vasculitis such as PAN, Schönlein–Henoch's purpura and Behçet's disease [39].

ASA Detection

The ability of sperm to induce antibodies has been documented for almost 50 years [68]. Approximately 10% of men undergoing evaluation for infertility will have antisperm antibodies in serum, seminal plasma, or else, directly attached to sperm [69].

The current consensus is that antibodies bound to sperm within the semen are the most important. Therefore, assays for sperm-bound antibodies are regarded to be the most appropriate. In addition, only IgG and IgA classes are found in significant quantities within the reproductive tract and should be included into the ASA assay [70].

The diagnosis of antibody-mediated infertility lacks a pathognomonic clinical picture. However, there are some parameters that guide an ASA assay recommendation [71]:

1. Agglutination or clumping in the absence of clinical infection in semen analysis
2. Low sperm motility usually less than 30% of total motility
3. Poor penetration of mucus on sperm–cervical mucus contact testing
4. Diagnosis of unexplained infertility

The most useful method for ASA detection are those that evaluate antibodies on the surface of spermatozoa [28] such as the direct immunobead binding test that detects antibodies on the sperm cell surface to Fc portion of the ASA (sperm head, mid-piece, and/or tail) using immunobeads rabbit anti-human Ig (IgA, IgG, and IgM). At least 50% of the motile spermatozoa must be coated with immunobeads in order to validate the clinical significance of test. Negative control should have a score <10% bead attachment and positive control a score >20% bead attachment [72]. Alternatively, there is other more economical tests that may be used for screening [30] that employs sheep erythrocytes instead of immunobeads to detect and localize antibody-bound sperm. Additional methodologies to detect ASA in infertile males include postcoital test and the hemizona assay [28]. However, independent of the methodology used, the lower limit of detection of sperm antibodies is not known compromising the clinical relevance of these assays.

Imaging

Several different imaging methods can be used for the diagnosis of orchitis, such as color Doppler sonography

and magnetic resonance imaging [8], and they are essential for the differential diagnosis with testicular torsion [73] and intrascrotal masses (abscesses, tumors, and hydroceles) [39].

Regarding autoimmune diseases, it has been observed that serial sections of affected testicles have uniform lesions, and therefore, a 3×3×3-mm biopsy should be sufficient to detect testicular manifestations [39]. Surgical complications of testicular biopsies are rare since minimal hematomas or infections are detected in less than 2% of this procedure [25, 39]. Furthermore, the risks for an immune response of clinical significance for fertility after biopsies are also low [39].

Treatment

Symptomatic patients with orchitis should receive analgesic treatment associated with local cooling, scrotal elevation, and bed rest [25]. Local anesthesia by a nerve block using 5 ml of 1% lidocaine around spermatic vessels may be necessary for those with severe tenderness; however, this procedure will not last longer [39].

In secondary autoimmune orchitis with or without testicular vasculitis, glucocorticoids [40], immunosuppressive agents (such as azathioprine and cyclophosphamide) [16, 37, 45, 57], and intravenous immunoglobulin [7] have been described as treatment options. Dapsone has been reported to be useful in Behçet's disease [74]. The impact of untreated testicular vasculitis on gonadal function and fertility is unknown; however, it seems to be relevant [25].

On the other hand, the treatment of infertility and the real significance of ASA are controversial, and there are no standardized treatment protocols. In uncontrolled studies of ASA-mediated infertility in males, oral glucocorticoids (commonly used to suppress antibody production) and non-steroidal anti-inflammatory drugs had been reported to have beneficial effects [23, 75]. The adverse events of glucocorticoids [30], however, particularly the risk of hip osteonecrosis, makes this option unattractive to most infertile couples [31]. One study described a significant increase in the number of pregnancies amongst those receiving prednisolone (20 mg twice daily on days 1–10 of the female partner's menstrual cycle, followed by 5 mg on days 11 and 12) for more than 3 months compared to placebo group [76]. Immunoinfertility treatment also includes other immunosuppressive agents, such as cyclosporine [77].

Sperm-washing technique can be used to remove bound antibody in assisted reproductive technique. Rapid dilutional washing of the seminal fluid may remove unbound antibodies; however, antibodies that are already bound will suffer little impact due [78].

Assisted reproductive technologies such as intrauterine insemination (IUI), in vitro fertilization (IVF), and ICSI are options therapy for male infertility due to the presence of ASA [28, 30, 77]. The conception rate per cycle was 3–10% by IUI with untreated semen [28]. A significant improvement was obtained using sperm sample collected in sterile medium from males with high levels of ASA (predominantly IgG antibodies). In fact, successful pregnancies were observed in 64% of couples after three IUI cycles, with 47% conception rate following the first cycle [79]. These benefits for immune infertility needs, however, to be defined in randomized prospective studies of IUI. When IVF is used to treat immune infertility in cases of male-factor infertility, early embryonic cleavage, the fertilization, and pregnancy rates was found to be lower than those observed for other indications, with overall pregnancy rates ranging from 14% to 35% per cycle [80]. However, in cases of female-derived ASA, IVF offers fertilization and pregnancy rates comparable to those associated with other diagnoses usually indicated for IVF procedure [81, 82].

ICSI seems to be a promising alternative for patients who failed IUI or IVF [28, 31]. This technique is also considered to be the treatment of choice for patients with severe sperm autoimmunity [2], particularly in males with low semen counts or motility [83]. Using ICSI, the numerical sperm requirement for egg fertilization is as low as one viable sperm for each retrieved oocyte [84]. This technology has the potential to overcome antibody-mediated infertility by bypassing the interaction between sperm and the zona pellucida as well as oocyte membrane [85]. The pregnancy success rates for ASA-positive infertile men were reported to be within the same range as population of ICSI patients with severely abnormal seminal parameters [86–88]. However, the same studies showed that embryo quality is poorer in ASA-positive than in ASA-negative ICSI cases, suggesting that ASA may affect post-fertilization events. Nonetheless, antisperm antibody testing has low sensitivity in predicting low fertilization and does not appear to be cost-effective when selectively ordered as part of an IVF workup in clinical settings at this time [89].

Future Directions

In spite of the major advances in understanding the underlying mechanism of autoimmune orchitis, there are at least a few areas of research progress that we expect in the near future. The first is a reliable, standardized testing protocol for antisperm antibodies, which will clarify the real contribution of this immunologic phenomenon in male infertility. The focus on genomic integrity, particularly the degree of DNA damage, and its possible association with autoimmune orchitis or

antisperm antibodies has not previously evaluated and may be the missed link of translating molecular alterations from bench to bedside. Finally, research directed at a better identification of underlying mechanism of autoimmune orchitis will certainly provide a more precise target therapy for these patients.

Acknowledgments This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP (grants 2004/07832-2 and 2005/56482-7 to CAS, and 2009/51897-5 to EB), Conselho Nacional de Desenvolvimento Científico e Tecnológico-CNPQ (grants 300248/2008-3 to CAS, 303165/2008-1 to EFB and 301411/2009-3 to EB) and Federico Foundation Grants to CAS, EFB, and EB.

References

1. Silva CA, Brunner HI (2007) Gonadal functioning and preservation of reproductive fitness with juvenile systemic lupus erythematosus. Lupus 16:593–599
2. Silva CA, Bonfa E, Ostensen M (2010) Maintenance of fertility in patients with rheumatic diseases needing anti-inflammatory and immunosuppressive drugs. Arthritis Care Res (Hoboken) 62:1682–1690
3. Revel A, Revel-Vilk S (2008) Pediatric fertility preservation: is it time to offer testicular tissue cryopreservation? Mol Cell Endocrinol 282:143–149
4. Silva CA, Hallak J, Pasqualotto FF, Barba MF, Saito MI, Kiss MH (2002) Gonadal function in male adolescents and young males with juvenile onset systemic lupus erythematosus. J Rheumatol 29:2000–2005
5. Suehiro RM, Borba EF, Bonfa E, Okay TS, Cocuzza M, Soares PM, Silva CA (2008) Testicular Sertoli cell function in male systemic lupus erythematosus. Rheumatology (Oxford) 47:1692–1697
6. Moraes AJ, Pereira RM, Cocuzza M, Casemiro R, Saito O, Silva CA (2008) Minor sperm abnormalities in young male postpubertal patients with juvenile dermatomyositis. Braz J Med Biol Res 41:1142–1147
7. Sallum AM, Garcia AJ, Saito OC, Silva CA (2009) Scrotum and testicular calcinosis in juvenile dermatomyositis (JDM). A report of two cases. Clin Exp Rheumatol 27:382–383
8. Moraes AJ, Bonfa E, Cocuzza M, Borges CT, Saito O, Silva CA (2010) Gonad evaluation in male dermatomyositis. A pilot study. Clin Exp Rheumatol 28:441–442
9. Balen AH, Rutherford AJ (2007) Management of infertility. BMJ 335:608–611
10. Rowe T (2006) Fertility and a woman's age. J Reprod Med 51:157–163
11. Bong GW, Koo HP (2004) The adolescent varicocele: to treat or not to treat. Urol Clin North Am 31:509–515, ix
12. Folomeev M, Alekberova ZS (1990) Impotence in systemic lupus erythematosus. J Rheumatol 17:117–119
13. Athreya BH, Rafferty JH, Sehgal GS, Lahita RG (1993) Adenohypophyseal and sex hormones in pediatric rheumatic diseases. J Rheumatol 20:725–730
14. Vilarinho ST, Costallat LT (1998) Evaluation of the hypothalamic-pituitary-gonadal axis in males with systemic lupus erythematosus. J Rheumatol 25:1097–1103
15. Mok CC, Lau CS (2000) Profile of sex hormones in male patients with systemic lupus erythematosus. Lupus 9:252–257
16. Walker G, Merry P, Sethia K, Ball RY (2000) A case of testicular lupus. Lupus 9:397–398
17. Latta K, von Schnakenburg C, Ehrich JH (2001) A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol 16:271–282
18. Meistrich ML, Wilson G, Brown BW, da Cunha MF, Lipshultz LI (1992) Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. Cancer 70:2703–2712
19. Ostensen M, Lockshin M, Doria A, Valesini G, Meroni P, Gordon C, Brucato A, Tincani A (2008) Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. Rheumatology (Oxford) 47(Suppl 3):iii28–iii31
20. Ostensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, Doria A, Rai R, Meroni P, Cetin I, Derksen R, Branch W, Motta M, Gordon C, Ruiz-Irastorza G, Spinillo A, Friedman D, Cimaz R, Czeizel A, Piette JC, Cervera R, Levy RA, Clementi M, De Carolis S, Petri M, Shoenfeld Y, Faden D, Valesini G, Tincani A (2006) Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 8:209
21. Vecchi AP, Borba EF, Bonfa E, Cocuzza M, Pieri P, Kim CA, Silva CA (2011) Penile anthropometry in systemic lupus erythematosus. Lupus 20:512–518
22. Soares PM, Borba EF, Bonfa E, Hallak J, Correa AL, Silva CA (2007) Gonad evaluation in male systemic lupus erythematosus. Arthritis Rheum 56:2352–2361
23. Schuppe HC, Meinhardt A, Allam JP, Bergmann M, Weidner W, Haidl G (2008) Chronic orchitis: a neglected cause of male infertility? Andrologia 40:84–91
24. Østensen M, Brucato A, Carp H, Chambers C, Dolhain R, Doria A, Förger F, Gordon C, Hahn S, Khamashta M, Lockshin M, Matucci-Cerinic M, Meroni PL, Nelson JL, Parke A, Petri M, Ruiz-Irastorza G, Raio L, Silva CA, Tincani A, Villiger PM, Wunder D, Cutolo M (2010) Pregnancy and reproduction in autoimmune rheumatic diseases. Rheumatology (Oxford) 50:657–664
25. Silva CA, Borba E, Cocuzza M, Carvalho J, Bonfá E (2008) Autoimmune orchitis. In: Shoenfeld Y, Gershwin ME (eds) Diagnostic criteria in autoimmune diseases, 1st edn. Springer Science, California, pp 281–284
26. Fijak M, Meinhardt A (2006) The testis in immune privilege. Immunol Rev 213:66–81
27. Krause W (2008) Male accessory gland infection. Andrologia 40:113–116
28. Shibahara H, Koriyama J, Shiraishi Y, Hirano Y, Suzuki M, Koyama K (2009) Diagnosis and treatment of immunologically infertile women with sperm-immobilizing antibodies in their sera. J Reprod Immunol 83:139–144
29. Taneichi A, Shibahara H, Hirano Y, Suzuki T, Obara H, Fujiwara H, Takamizawa S, Sato I (2002) Sperm immobilizing antibodies in the sera of infertile women cause low fertilization rates and poor embryo quality in vitro. Am J Reprod Immunol 47:46–51
30. Agarwal A, Bragais FM, Sabanegh E (2008) Assessing sperm function. Urol Clin North Am 35:157–171, vii
31. Shefi S, Turek PJ (2006) Definition and current evaluation of subfertile men. Int Braz J Urol 32:385–397
32. Arap MA, Vicentini FC, Cocuzza M, Hallak J, Athayde K, Lucon AM, Arap S, Srougi M (2007) Late hormonal levels, semen parameters and presence of antisperm antibodies in patients treated for testicular torsion. J Androl 28:528–532
33. Bhasin S (2007) Approach to the infertile man. J Clin Endocrinol Metab 92:1995–2004
34. Shiraishi Y, Shibahara H, Koriyama J, Hirano Y, Okazaki H, Minota S, Suzuki M (2009) Incidence of antisperm antibodies in males with systemic autoimmune diseases. Am J Reprod Immunol 61:183–189
35. D'Cruz OJ, Haas GG Jr, Reichlin M (1994) Autoantibodies to decondensed sperm nuclear deoxyribonucleic acid in patients

with antisperm antibodies and systemic lupus erythematosus detected by immunofluorescence flow cytometry. Fertil Steril 62:834–844
36. Kuehn MW, Oellinger R, Kustin G, Merkel KH (1989) Primary testicular manifestation of systemic lupus erythematosus. Eur Urol 16:72–73
37. MacIver H, Hordon L (2009) An unusual case of testicular pain. Clin Rheumatol 28:351–352
38. Boulis ER, Majithia V (2011) Orchitis in lupus/scleroderma overlap syndrome: a case report and literature review. Can J Urol 17:5306–5308
39. Pannek J, Haupt G (1997) Orchitis due to vasculitis in autoimmune diseases. Scand J Rheumatol 26:151–154
40. Pastor-Navarro H, Broseta-Viana L, Donate-Moreno MJ, Pastor-Guzman JM, Lorenzo-Romero JG, Segura-Martin M, Salinas-Sanchez AS, Virseda-Rodriguez JA (2007) Isolated testicular polyarteritis nodosa. Urology 70(178):e7–e8
41. Persellin ST, Menke DM (1992) Isolated polyarteritis nodosa of the male reproductive system. J Rheumatol 19:985–988
42. Fraenkel-Rubin M, Ergas D, Sthoeger ZM (2002) Limited polyarteritis nodosa of the male and female reproductive systems: diagnostic and therapeutic approach. Ann Rheum Dis 61:362–364
43. Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, Bienvenu B, Mouthon L, Guillevin L (2010) Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum 62:616–626
44. Kaklamani VG, Vaiopoulos G, Markomichelakis N, Kaklamanis P (2000) Recurrent epididymo-orchitis in patients with Behcet's disease. J Urol 163:487–489
45. de Almeida JL, Campos LM, Paim LB, Leone C, Koch VH, Silva CA (2007) Renal involvement in Henoch–Schonlein purpura: a multivariate analysis of initial prognostic factors. J Pediatr (Rio J) 83:259–266
46. Ha TS, Lee JS (2007) Scrotal involvement in childhood Henoch–Schonlein purpura. Acta Paediatr 96:552–555
47. Fijak M, Bhushan S, Meinhardt A (2011) Immunoprivileged sites: the testis. Methods Mol Biol 677:459–470
48. Guazzone VA, Jacobo P, Theas MS, Lustig L (2009) Cytokines and chemokines in testicular inflammation: a brief review. Microsc Res Tech 72:620–628
49. Fijak M, Iosub R, Schneider E, Linder M, Respondek K, Klug J, Meinhardt A (2005) Identification of immunodominant autoantigens in rat autoimmune orchitis. J Pathol 207:127–138
50. Rival C, Guazzone VA, Theas MS, Lustig L (2005) Pathomechanism of autoimmune orchitis. Andrologia 37:226–227
51. Hedger MP, Meinhardt A (2003) Cytokines and the immune-testicular axis. J Reprod Immunol 58:1–26
52. Jacobo P, Guazzone VA, Theas MS, Lustig L (2011) Testicular autoimmunity. Autoimmun Rev 10:201–204
53. Filippini A, Riccioli A, Padula F, Lauretti P, D'Alessio A, De Cesaris P, Gandini L, Lenzi A, Ziparo E (2001) Control and impairment of immune privilege in the testis and in semen. Hum Reprod Update 7:444–449
54. Theas S, Rival C, Lustig L (2003) Germ cell apoptosis in autoimmune orchitis: involvement of the Fas-FasL system. Am J Reprod Immunol 50:166–176
55. Wu H, Wang H, Xiong W, Chen S, Tang H, Han D (2008) Expression patterns and functions of toll-like receptors in mouse sertoli cells. Endocrinology 149:4402–4412
56. Naito M, Itoh M (2008) Patterns of infiltration of lymphocytes into the testis under normal and pathological conditions in mice. Am J Reprod Immunol 59:55–61
57. Mayer DF, Matteson EL (2004) Testicular involvement in rheumatoid vasculitis. Clin Exp Rheumatol 22:S62–S64
58. Agarwal A, Said TM (2005) Oxidative stress, DNA damage and apoptosis in male infertility: a clinical approach. BJU Int 95:503–507
59. Cocuzza M, Sikka SC, Athayde KS, Agarwal A (2007) Clinical relevance of oxidative stress and sperm chromatin damage in male infertility: an evidence based analysis. Int Braz J Urol 33:603–621
60. Sakkas D, Mariethoz E, Manicardi G, Bizzaro D, Bianchi PG, Bianchi U (1999) Origin of DNA damage in ejaculated human spermatozoa. Rev Reprod 4:31–37
61. Henkel R, Hajimohammad M, Stalf T, Hoogendijk C, Mehnert C, Menkveld R, Gips H, Schill WB, Kruger TF (2004) Influence of deoxyribonucleic acid damage on fertilization and pregnancy. Fertil Steril 81:965–972
62. Agarwal A, Allamaneni SS (2004) The effect of sperm DNA damage on assisted reproduction outcomes. A review. Minerva Ginecol 56:235–245
63. Tomsu M, Sharma V, Miller D (2002) Embryo quality and IVF treatment outcomes may correlate with different sperm comet assay parameters. Hum Reprod 17:1856–1862
64. Eggert-Kruse W, Hofsass A, Haury E, Tilgen W, Gerhard I, Runnebaum B (1991) Relationship between local anti-sperm antibodies and sperm-mucus interaction in vitro and in vivo. Hum Reprod 6:267–276
65. Omu AE, al-Qattan F, Mohammed A (1996) Expression of human leukocyte antigens in patients with autogenic and allogenic circulating antisperm antibodies. Arch Androl 37:155–162
66. Rumke P, Hellinga G (1959) Autoantibodies against spermatozoa in sterile men. Am J Clin Pathol 32:357–363
67. Practice Committee of the American Society for Reproductive Medicine (2006) Definition of "infertility". Fertil Steril 86:S228
68. Billingham RE, Brent L, Medawar PB (1953) Actively acquired tolerance of foreign cells. Nature 172:603–606
69. Hendry WF, Morgan H, Stedronska J (1977) The clinical significance of antisperm antibodies in male subfertility. Br J Urol 49:757–762
70. Hendry WF (1992) The significance of antisperm antibodies: measurement and management. Clin Endocrinol (Oxf) 36:219–221
71. Walsh TJ, Turek PJ (2009) Immunologic infertility. In: Lipshultz LI, Stuart SH, Niederberger CS (eds) Infertility in the male, 4th edn. Cambridge University Press, United Kingdom, pp 277–294
72. WHO (1999) World Health Organization: WHO Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. Cambridge University Press, New York
73. Prando D (2009) Torsion of the spermatic cord: the main gray-scale and Doppler sonographic signs. Abdom Imaging 34:648–661
74. Sharquie KE (1984) Suppression of Behcet's disease with dapsone. Br J Dermatol 110:493–494
75. Haidl G (2002) Management strategies for male factor infertility. Drugs 62:1741–1753
76. Hendry WF, Hughes L, Scammell G, Pryor JP, Hargreave TB (1990) Comparison of prednisolone and placebo in subfertile men with antibodies to spermatozoa. Lancet 335:85–88
77. Naz RK (2004) Modalities for treatment of antisperm antibody mediated infertility: novel perspectives. Am J Reprod Immunol 51:390–397
78. Adeghe AJ (1987) Effect of washing on sperm surface autoantibodies. Br J Urol 60:360–363
79. Ombelet W, Vandeput H, Janssen M, Cox A, Vossen C, Pollet H, Steeno O, Bosmans E (1997) Treatment of male infertility due to sperm surface antibodies: IUI or IVF? Hum Reprod 12:1165–1170
80. Turek PJ, Lipshultz LI (1994) Immunologic infertility. Urol Clin North Am 21:447–468
81. Daitoh T, Kamada M, Yamano S, Murayama S, Kobayashi T, Maegawa M, Aono T (1995) High implantation rate and consequently high pregnancy rate by in vitro fertilization-

embryo transfer treatment in infertile women with antisperm antibody. Fertil Steril 63:87–91
82. Vazquez-Levin MH, Notrica JA, Polak de Fried E (1997) Male immunologic infertility: sperm performance on in vitro fertilization. Fertil Steril 68:675–681
83. Check JH (2007) Treatment of male infertility. Clin Exp Obstet Gynecol 34:201–206
84. Junk SM, Matson PL, Yovich JM, Bootsma B, Yovich JL (1986) The fertilization of human oocytes by spermatozoa from men with antispermatozoal antibodies in semen. J In Vitro Fert Embryo Transf 3:350–352
85. Kamada M, Yamano S, Senuma M, Nakagawa K, Maegawa M, Aono T (1998) Semen analysis and antisperm antibody. Arch Androl 40:117–128
86. Esteves SC, Schneider DT, Verza S Jr (2007) Influence of antisperm antibodies in the semen on intracytoplasmic sperm injection outcome. Int Braz J Urol 33:795–802
87. Nagy ZP, Verheyen G, Liu J, Joris H, Janssenswillen C, Wisanto A, Devroey P, Van Steirteghem AC (1995) Results of 55 intracytoplasmic sperm injection cycles in the treatment of male-immunological infertility. Hum Reprod 10:1775–1780
88. Lahteenmaki A, Reima I, Hovatta O (1995) Treatment of severe male immunological infertility by intracytoplasmic sperm injection. Hum Reprod 10:2824–2828
89. Culligan PJ, Crane MM, Boone WR, Allen TC, Price TM, Blauer KL (1998) Validity and cost-effectiveness of antisperm antibody testing before in vitro fertilization. Fertil Steril 69:894–898