Diagnosis and treatment of immunologically infertile males with antisperm antibodies

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The presence of antisperm antibodies (ASA) can reduce fecundity in both males and females. The present review describes a strategy, established by investigations of the diverse inhibitory effects of ASA on fertility, for the appropriate diagnosis and treatment of infertile males with ASA. For infertile males with ASA, diagnosis using the direct-immunobead test (D-IBT), the postcoital test (PCT) and the hemizona assay (HZA) should be carried out as the basis for decision-making. If the patient with ASA has an abnormal hemizona index, it seems reasonable to advise selecting intracytoplasmic sperm injection-embryo transfer (ICSI-ET) as a primary treatment. However, it has been shown that some immunologically infertile males with normal fertilizing ability established pregnancy by timed intercourse (TI) or intrauterine insemination (IUI). In such patients with ASA having normal hemizona index, TI or IUI can be selected based on the PCT result. Therefore, the treatment strategy for males with ASA is similar to that for infertile males with oligozoospermia or asthenozoospermia.

In conclusion, it should be emphasized that a diversity of ASA exists and their effects on fertility in infertile males. Although there is an argument that routine testing for ASA in males is not always necessary, one should be aware that in some cases of failed IUI or IVF, ICSI is selected afterward because of the diagnosis of ASA. (Reprod Med Biol 2005; 4: 133–141)

Key words: antisperm antibodies, in vitro fertilization, intracytoplasmic sperm injection, intrauterine insemination, postcoital test.

INTRODUCTION

The presence of naturally occurring antibodies against antigens in the gametes can reduce fecundity in both males and females. Although antioocyte and antizona-pellucida antibodies are not found frequently in females, it is well known that antisperm antibodies (ASA) play important roles in male and female immunological infertility. In infertile males, ASA may be detected in seminal plasma and serum, and may also be located on the surface of spermatozoa. However, the relationship between the presence of ASA in males and infertility continues to be disputed, in part because a standardized and universally accepted assay for the detection of ASA, consensus about the clinical consequences of ASA, and a mechanistic explanation of how ASA impairs conception in immunologically infertile men remain unestablished.

The authors have recently demonstrated that there is a diversity of ASA bound to the sperm surface, including different immunoglobulin (Ig) classes of ASA, differing localization of the corresponding antigens for ASA, and different biological activities of ASA, in males. Moreover, a relatively high incidence of asthenozoospermia was demonstrated in immunologically infertile males, and a significant effect of sperm-immobilizing antibodies bound to the surface of ejaculated sperm on sperm motility was confirmed.

The present review describes a strategy, based on these investigations of the diverse inhibitory effects of ASA bound to the sperm surface on fertility, for the diagnosis and treatment of infertile males with ASA.

Production of antisperm antibodies in males

It has been postulated that the development of autoimmunity to sperm may be prevented by the sequestration of autoantigens in germ cells by the presence of the blood–testis barrier. A study has documented the presence of ASA and orchitis following testicular regression and breakdown of the blood–testis barrier in the dark mink. In mice, it has been shown that autoantigenic
germ cells exist outside of the blood–testis barrier and are accessible to antigen-processing cells, suggesting that active local immunoregulatory mechanisms may be operative within the testis.9–11

In humans, an autoimmune condition can also develop, leading to the production of ASA that react with sperm. However, most cases of sperm autoimmunity are spontaneous, or idiopathic. The condition of having ASA has been found in homosexual males,12,13 and in cases of testicular trauma,14 varicocele,15 mumps orchitis,16 spinal cord injury,17 congenital absence of the vas,18 and vasectomy.19–21 Therefore, developmental abnormalities of the formation of the blood–testis barrier and traumatic disruption of this barrier can lead to ASA formation in males.

Concerning human leukocyte antigen (HLA) gene types in women with ASA, Tsuji et al.22 have shown that patients having sperm-immobilizing antibodies in their sera had significantly higher frequencies of HLA-DRB1*0901 and HLA-DQB1*0303. In males with circulating ASA, the HLA class II pattern was investigated and it was found that DR6 and DQ7 were more common.23 However, little is known about the relationship between the susceptibility to ASA and the surface features of sperm or the HLA gene type.24

Causes of infertility due to antisperm antibodies in males

The causes of infertility due to ASA in females have been well clarified. Our group demonstrated that ASA, especially sperm-immobilizing antibodies discovered by Isojima et al.24 can impair sperm migration in the female genital tract, in particular in the cervical mucus25 and the uterine cavity through the Fallopian tubes.26 We also reported the inhibitory effects of sperm-immobilizing antibodies on fertilization,27–31 and postfertilization events.30–33

Similarly, it has been shown that sperm that are antibody-bound over most of their surfaces are unable to enter the cervical mucus, antibody binding to the sperm tail tip being an exception.28 Ayvaliotis et al. also reported that when all sperm were coated with Ig, it was rare to find sperm within the cervical mucus, despite the presence of hundreds of millions of motile sperm in the ejaculate.35 The number of motile sperm observed in the cervical mucus increased as the proportion of antibody-coated sperm declined below 50%, as judged by immunobead binding. These observed impairments of the ability of sperm to penetrate through the cervical mucus appears to be mediated by the effector region (Fc) portion of the Ig molecules.36,37 The Ig possess both an antigen-recognition region (Fab) and an Fc that binds to various leukocytes through specific surface receptors (FcR).38 Sperm exposed to the Fab portion of IgG of ASA can swim through the cervical mucus, whereas those exposed to intact IgG of ASA can not.

The ASA in males have also been shown to have an inhibitory effect on fertilization.39–43 The possibility exists that fertilization-related antigens may be the targets of these ASA. Such antigens consisted of sperm surface antigens and acrosomal antigens. The former include PH-20,44,45 PH-30,46–48 fertilization antigen-1 (FA-1),49–51 sperm agglutination antigen-1 (SAGA-1),52–54 and lactate dehydrogenase-C4 (LDH-C4),55,56 and the latter includes SP-10.54,57

The PH-20 is a peripheral membrane glycoprotein (with 56 kDa and 64 kDa forms) implicated in gamete interaction.44 It has important roles in sperm-zona pellucida (ZP) penetration as well as in sperm-ZP binding. Gmachl et al. reported the cloning of human PH-20 and showed its homology with bee venom hyaluronidase.55 They demonstrated that recombinant PH-20 exhibits hyaluronidase activity.

The PH-30 antigen is another postacrosomal plasma membrane antigen.46 Myles et al. designated the PH-30 antigen as fertilin, based on its apparent role during fertilization.47 The fertilin β subunit (44 kDa) functions as a ligand for integrins on the egg surface, while fertilin α (60 kDa) is responsible for gamete membrane fusion.48

The FA-1 was identified as a dimeric glycoprotein (47 kDa) that binds to a monoclonal antibody (mAb) generated against human sperm.59 The Anti-FA-1 mAb completely inhibited human sperm penetration into zona-free hamster ova, significantly impaired IVF in mice and cattle, and inhibited capacitation and the acrosome reaction of human sperm.49–51

The SAGA-1 was characterized as a polymorphic, highly acidic, glycosylphosphatidylinositol-anchored glycoprotein (15–25 kDa) on the surface of human sperm.52 Diekman and colleagues63 independently generated a mAb, S19, against an antigen designated SAGA-1 via the immunization of mice with human sperm extracts. The S19 mAb impeded human sperm penetration into zona-free hamster ova and inhibited IVF in mice.54

The testis-specific isozyme LDH-C4 (140 kDa) functions in lactate metabolism and glycolysis of developing and mature sperm.55 Active immunization with LDH-C4 suppressed fertility in a variety of mammalian species, including female primates.55 A recent study showed that in mature male baboons immunized with a chimeric peptide containing a B-cell epitope of LDH-C4...