

Effects of Sperm Treatment on the Anti-sperm Antibodies IgG and IgA

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Abstract: Anti-sperm antibodies (ASA) form a class of glycoproteins commonly found in infertile men. This class of antibody causes an impairment of the spermatozoon's ability to cross cervical mucus and interact with the oocyte. The aim of our study was to analyze clinical and biological parameters of the sperm among positive ASA patients seen at the Center of Assisted Medical Procreation of the CHU Reunion before and after in-vitro treatment of autoimmune sperms. During the period from April 01, 2013 to February 29, 2015, we analyzed clinico-biological parameters of patients coming for exploring an infertility state with ASA IgG and IgA research before and after sperm treatment. Fourteen (1.51%) patients had a positive ASA, with a combination of ASA IgG and IgA for 71.42% of them. After in vitro treatment of the autoimmune sperm we found a persistence of IgA in 21.43% without IgG.

Keywords: Anti-Sperm Antibodies, Sperm Treatment, Réunion Island

1. Introduction

According to the World Health Organization, infertility is defined by the absence of pregnancy after at least 12 months of unprotected intercourse [1]. About one-third of the couple's infertility cases are male origin. The causes of male infertility are variable and include immunological causes. Anti-sperm antibodies (ASA) were detected in the 19th century by Metchnikoff, but the presence of human ASA was demonstrated by Nakabayashi *et al.*, in the 1960s [2]. These antibodies have been found in both men and women. These antibodies are either immunoglobulin A, secreted essentially at the level of the epididymis or immunoglobulin G, the most important class of antibody in the body. They may be immobilizing, agglutinating or cytotoxic, disrupting many of the steps required for normal fertilization by altering the mobility of spermatozoa and may thus have negative effects on fertility. On the other hand, some studies have shown that spermatogenesis is not affected by ASA [3]. ASA production is due to the breakdown of the blood-brain barrier and their interactions with immunocompetent cells resulting in the

passage of sperm antigens into the bloodstream. Elevated ASA levels are encountered in men with a history of torsion, vasectomy, orchiepididymitis, cryptosporidia, genital infections, urinary tract infections and chronic genital tract, trauma and surgery as well as testicular cancer. The present study aims to analyze the clinical and biological parameters of the sperm of the positive ASA patients seen at the Assisted Medical Procreation Center of the CHU Reunion before and after in-vitro treatment of autoimmune sperms.

2. Methods

A total of 1042 patients coming for exploration of an infertility balance were analyzed during the period from 01 April 2013 to 29 February 2015 at the Assisted Medical Procreation Center of the CHU *Saint-Pierre Réunion*. Several clinical parameters were analyzed including age, risk factors for immunological infertility such as vasectomy, vasectomy reversal, previous vasal obstruction (i.e., cystic fibrosis),

testicular torsion, testicular carcinoma, cryptorchidism, and genital tract infections (e.g., urethritis and epididymo-orchitis which implicate *HPV*, *Chlamydia*, *Cytomegalovirus* pathogens). Moreover, sperm parameters such as duration of abstinence, ejaculate volume, viscosity, sperm count, leukocyte counts, presence of agglutinates, vitality and spermocytogram according to WHO recommendations were also evaluated [4]. ASA was tested using the MAR test kit Ig A and Ig G Fertipro Belgium® in which we specified the antibody type, attachment level and ASA level (figure 1). According to the results of the ASA research, patients were classified in Group I for patients with IgG type ASA alone, group II for ASA type IgA alone and group III for both ASA type IgA and IgG. According to the recommendations of the manufacturer, patients are suspected of ASA if the ASA rate is between 10 to 39% and they are highly ASA probable if the rate is greater than 40 %. All patients with positive ASA were treated with discontinuous density gradient, according to the WHO 2010 recommendations [4] using the Sydney IVF Sperm Gradient reagents Cook Australia® one of the 40% density and one of the 80% density and then suspended in 300 µl of Sydney IVF Fertilization Medium Cook Australia®. The level and binding site of ASA IgA and IgG were then analyzed. Data were analyzed using the Microsoft Excel 2010 and the “R” softwares. Collection of documents and all measures were taken with the respect of strict confidentiality.

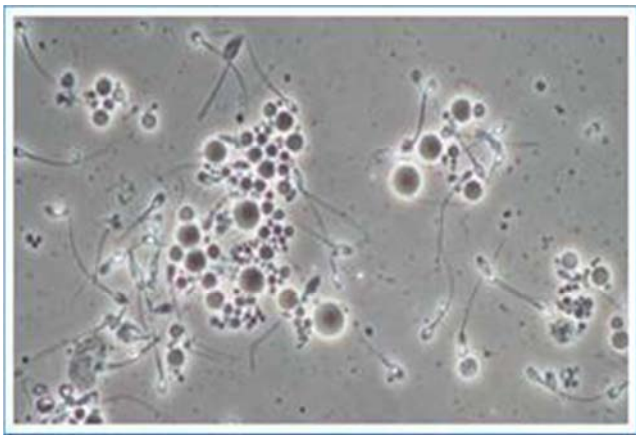


Figure 1. IgG Antisperm antibodies with flagellar localization.

3. Result

During the study period 1042 patients were analyzed and 14 (1.51%) patients had a positive ASA. 28.57% of patients had ACAS risk factor with cryptorchidism type and genital infection but none had history of vasectomy. The spermatic parameters were normal for the majority of patients where as oligospermia, asthenospermia and the presence of agglutinates were reported in 14.29%. Concerning ASA, Group I represent 14.28% of patients, group II 14.28% of patients and group III 71.42% of patients (Table 1). Flagellar localization is the most frequent (87.71%) in both type antibodies and 14.28% had more than two localizations.

30.76% of patients were 100% ASA Ig G, 53.84% were between 40% and 99%, for ASA IgA 77.77% of patients were between 10% and 39%. After in vitro treatment of autoimmune sperm, IgA persistence was found in 21.43% with 83% IgG-free level in group III with flagellar localization. Assessment of the fertility index is greater than 1 million sperm capacities in 71.43%.

Table 1. Distribution of IgG and IgA in patients.

Group	Patients n: 14
Group I (IgG only)	2 (14,28%)
Group II (IgA only)	2 (14,28%)
Group III (IgA and Ig G)	10 (71,42%)

4. Discussion

The prevalence of antisperm antibodies in infertile men is about 5 to 10% whereas it is less than 1% in fertile men [3]. In our study, it represented only 1.51% of patients. From the etiological point of view, vasectomy is the main etiological factor in ASA, with half of the men whose deferens has been ligated develop immobilizing or agglutinating ASAs [5]. Numerous studies demonstrated that there are viral, bacterial and fungal particles capable of attaching to the spermatozoa membrane and behaving as a vector encouraging the immune system to react against these own molecules. [6] Indeed, *Blanc and Boubli* (2003) indicate that 30% of men with an infection develop ASA [5]. However, a study by *Marconi et al.* (2008) on 133 patients showed no association between inflammations or genital tract infections and MAR Test/IBT results [7]. In addition, *Wolff et al.* (1990) did not demonstrate a relationship between leucospermia and the onset of ASA [8]. Among other etiologies, we can evoke the varicocele, the cryptorchidia [9] but rarely testicular tumors [10]. However, many men with no pathological history develop ASA and the occurrence of pregnancy in couples whose man is ASA makes the incrimination of this immunological concept in regard of infertility a relative and variable facts depending on the rate, isotype, site of fixation and action of ASA [11]. The presence of ASA in humans results in disruption of many stages necessary for normal fertilization and can thus have negative effects on fertility, beginning with the agglutination of spermatozoa [12], disturbing their mobility, and may also have acytotoxic effect on spermatozoa through the activation of the classical complement pathway and the formation of the membrane attack complex (CAM) leading to their cytolysis which consequently decrease spermatozoa's number.

Additionally, ASA can also inhibit sperm capacitation and penetration in cervical mucus (IgA-related property) causing their inability to penetrate the zonapellucida; and causing disturbance of the implantation of the egg [13]. However, other studies shown that spermatogenesis is not affected by ASA. The decrease in the pregnancy rate in ACAS is confirmed by *Meinertz et al.* (1990) who studied the rate of pregnancies after surgical repair of a vasectomy showing that in the presence of IgG alone, the pregnancy rate is 85.7%; In

the presence of IgA alone, the recorded pregnancy rate was 42.9%; If all the spermatozoa are covered with IgA, the pregnancy rate decreases by half to 21.7%; The pregnancy rate becomes zero in an isotypic association with a high level of serum IgG [14]. Sperm preparation techniques, based on the density gradient used in intrauterine insemination (IUI) are among the first-line techniques in ASA. *Mahmoud and Comhaire* (2000), recorded a pregnancy rate of 8.6% per IUI cycle. From the point of view of price effectiveness, the IUI remains the therapy of choice in some cases of immunological infertility. The use of chymotrypsin, a digestive enzyme manufactured by the pancreas before IUI with sperm samples showing 100% spermatozoa coated with antibodies, gave a pregnancy rate of 11% per IUI cycle [15]. However, it remains to be demonstrated that the persistence of the Fab portion of the antibodies (not digested by the proteases) does not prevent the interaction with the oocyte and especially that the enzymes used do not have deleterious effect on the fertilizing power of gamete.

This decrease was related to both IgA and IgG, but overall, only IgG was significantly decreased. After a failure of three cycles of artificial insemination, the use of in vitro fertilization (IVF) resulted in a better pregnancy rate, especially if the ASA rate exceeded 50% with predominant IgG. However, in the most severe cases the Intracytoplasmic Sperm Injection (ICSI) is generally recommended. Indeed, *Naggy et al.* (1995) demonstrated that there was no significant difference of pregnancy rates resulting from ICSI practice with antibody levels above 80% and those with negative ASA tests. However, the number of poor quality embryos was higher among those with ASAs greater than 80% [17]. If the sperm parameters are normal according to the recommendations of the WHO 2010, the preparation of semen in view IUI is recommended, in case where the parameters are deleterious the therapeutic indication are the IVF and ICSI. It is shown that the spermatozoa are all or nearly all (> 70%) coated by ASA will suffer clinically for infertility [15] [18]. Furthermore, when 100% of sperm have ASA attached, intrauterine insemination (IUI) completely failed to achieve pregnancies. In regard of antibodies class, it is assumed that the only presence of IgG fixed on the spermatozoa is better prognosis than the presence of IgA isolated or not [19]. In fact, the IgA would impede the penetration of cervical mucus. In regard of antibodies' fixation site, it is natural to suppose that a flagellar fixation inhibits the penetration of the female genital tract, while a fixation on the head of the spermatozoon tends to reduce the penetration of the oocyte pellucid zone. Indeed, the impact of antibodies on spermatid functions depends not only on their level but also on their class and antigenic specificity [20]. The responsibility of autoantibodies in the low fertilizing power of spermatozoa is clear when more than 80% of ejaculated sperm or 70% of the inseminated spermatozoa are covered with antibodies of the 2 IgA and IgG classes. Under these conditions, the failure of intrauterine insemination was observed and only 14 to 24% of the oocytes were fertilized in the IVF.

5. Conclusion

The treatment of autoimmune sperm remains a therapeutic alternative as this technique is easier and cheaper, but its indication must be limited to a rate of ASAIgG and / or Ig A less than 70%, with disappearance of ASA after treatment of sperm.

Disclosure of Interest

The authors declare that they have no conflicts of interest concerning this article.

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