

## ORIGINAL ARTICLE

# Testing for hypersensitivity to seminal fluid-free spermatozoa

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### Abstract

Hypersensitivity to human semen (HHS) is an increasingly reported condition with symptoms manifested locally and systemically, which in some cases may result in anaphylaxis. This report describes four cases of HHS all with positive allergy skin prick tests to partner's whole semen. None of the patients elicited a response to seminal fluid-free washed spermatozoa. In cases of high risk of anaphylaxis, we recommend avoiding exposure to semen. By carrying out an allergy skin prick test on seminal fluid-free washed spermatozoa, the risk of immunogenic reaction to the spermatozoa could be eliminated.

### Introduction

Allergies to semen or hypersensitivity to human semen (HHS) was first documented in the late 1950s (Ludman, 1999; Bernstein, 2011). Since then there have been numerous reports of this condition from various countries (Shah & Panjabi, 2004), but the true prevalence is unknown. However, HHS is usually reported as a rare condition (Lee et al., 2008; Tomitaka et al., 2002).

HHS is an IgE-mediated allergic reaction to specific components of seminal plasma, most likely, prostate glycoproteins, rather than spermatozoa (Reunala et al., 1977; Weidinger et al., 2005).

Women aged 20–30 years are most affected, displaying symptoms immediately or up to 1 h after exposure. Local reactions include itching, erythema and oedema in the vulvar region, or other areas, which have been in contact with semen. Systemic reactions include dyspnoea, dysphagia, rhinoconjunctivitis, generalised urticaria, angioedema, gastrointestinal symptoms, and exacerbation of atopic eczema (Bernstein et al., 1981; Shah & Panjabi, 2004) and in severe cases, anaphylaxis (Tomitaka et al., 2002; Lee et al., 2008). However, in all reported cases of HHS, the use of condoms prevented the symptoms (Shah & Panjabi, 2004; Bernstein, 2011).

The diagnosis of HHS is based on a careful history, a serological testing for specific IgE to seminal proteins

and a skin prick test (SPT) using semen or seminal fluid fractions (Lee-Wong et al., 2008; Bernstein, 2011). The symptoms of HHS are often overlooked or misdiagnosed. This may be due to a lack of recognition and the similarity of HHS symptoms to other conditions such as contact dermatitis (Guillet & Dagregorio, 2004), sexually transmitted infections (STIs), vulvovaginitis (Shah & Panjabi, 2004), or the transfer of food allergens through semen to a sexual partner allergic to these allergens (Bansal et al., 2007).

Therapeutic options include the use of condoms, prescription of antihistamines and attempts at desensitisation. Avoiding the allergen either by abstinence or with condom use is the best option in HHS cases, but this is not always acceptable for patients and their partners. There have been some reports of the prophylactic use of antihistamines (H1 and H2 antagonists) prior to coitus relieving some local symptoms (Jones, 1991). However, recent studies have reported that antihistamines can have adverse affects on ovulation (Agrawal & Jose, 2011) and embryo implantation (Agrawal & Jose, 2009) in animal models. The effects of antihistamines on human fertility have yet to be examined in any detail. Another treatment option for HHS, with varying degrees of success, is desensitisation by graded intravaginal challenge (Mittman et al., 1990; Matloff, 1993; Lee-Wong et al., 2008).

However, these options may not be suitable for every case of HHS.

We set out to investigate whether the women presented to our clinic showed an allergic reaction to clinical grade washed spermatozoa. The washed spermatozoa were free from seminal plasma components.

## Methods

Four women, aged between 19 and 29 years (referred to as patients A, B, C and D, respectively), were referred to the Department of Immunology at Central Manchester University Hospitals NHS Foundation Trust. Three women were of British white ethnicity (A, C and D) and one was of Asian (Indian) ethnicity (B). Each patient complained of symptoms such as itching, angioedema and a burning sensation in the vulva/vagina within minutes of exposure to semen, lasting for several hours. All four patients had specific IgE evaluated using a solid phase assay (ThermoFisher ImmunoCAP) prior to their visit (Table 1). This test was carried out using the serum from each woman against her partner's semen.

In the subsequent visit to the clinic, each patient's partner was given instructions on how to produce a semen sample for clinical use prior to their scheduled appointment. The sample was produced at home and brought into the clinic on the day of the allergy appointment. The spermatozoa in each sample were separated from the seminal fluid using density gradient centrifugation by overlaying 1 ml of neat semen over 1 ml of density gradient medium (SupraSperm System, Origio MediCult media, Denmark). This was centrifuged at 300 g for 20 min. The supernatant was discarded, and the pellet of sperm washed in 3 ml of wash medium (Sperm Preparation Medium, Origio MediCult media, Denmark) and centrifuged at 600 g for 5 min. The wash step was repeated. The pellet of washed sperm was resuspended in 0.5 ml of wash medium, and a 10- $\mu$ l sample placed on a glass slide and examined under phase contrast microscopy to ensure the presence of spermatozoa. Additional samples for the allergy prick test included neat semen, the density gradient media and the wash medium. The supernatant of seminal plasma was not

required for this investigation as all seminal plasma proteins are present in neat semen.

The allergy SPT was performed using the four samples (neat semen, washed spermatozoa, density gradient medium and wash medium). Each sample, plus positive (histamine, 10 mg/ml) and negative controls (sterile saline solution), was tested on the volar aspect of the forearm. The results were observed after 10–15 min. A cut-off of a wheal 2 mm wider than the negative control was used to designate a positive test result (Table 1).

## Results

Each woman tested showed a positive reaction to the allergy SPT for neat semen. However, none of them demonstrated any reaction to the washed spermatozoa or to the media used in the preparation (Table 1). *In vitro* testing for semen-specific IgE (Thermo Fisher ImmunoCAP) was negative in the samples tested, with one of them showing borderline significance (Table 1).

Our diagnostic criteria included a suggestive history, lack of other explanation for symptoms, a positive SPT, serum-specific IgE level (sIgE) and improvement on avoidance of exposure. Each of the women in this study did not display any symptoms of HHS with condom use.

## Discussion

All four women in this study showed a positive reaction to the SPT. The cut-off for SPT reactivity is generally recommended to be 3 mm, and on routine use, some SPTs can produce results of 20 mm or more. However, the difficulty encountered in the present study was that the specificity of our test could not be optimised by carrying out receiver operating characteristic curve analysis due to being unable to perform SPTs on asymptomatic women, with semen from unrelated men. Previous papers on semen allergy have described SPT cut-offs of 4 mm (Bernstein et al., 1993), but also patients with negative SPT and either positive intra-dermal tests (not carried out in this study) or blood IgE levels (Lee-Wong et al., 2008; Drouet et al., 1997).

Table 1. Semen allergy skin prick test results.

| Patient | Age | Atopic history                                                                   | Positive skin prick reaction to semen (size of wheal, mm) | *Serum-specific IgE          | Positive skin prick reaction to washed sperm (size of wheal, mm) | Positive skin prick reaction to media (size of wheal, mm) | Symptoms with condom use |
|---------|-----|----------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------|------------------------------------------------------------------|-----------------------------------------------------------|--------------------------|
| A       | 19  | No history of other allergies                                                    | Yes (3)                                                   | 2.0 (borderline significant) | No (0)                                                           | No (0)                                                    | No                       |
| B       | 29  | Hay fever                                                                        | Yes (3)                                                   | < 0.4 (negative)             | No (1)                                                           | No (0)                                                    | No                       |
| C       | 25  | Asthma, hay fever,                                                               | Yes (2)                                                   | N/A (not done)               | No (0)                                                           | No (0)                                                    | No                       |
| D       | 28  | Mild eczema, food allergies, latex allergy, dust mite and insect venom allergies | Yes (2)                                                   | < 0.4 (negative)             | No (0)                                                           | No (0)                                                    | No                       |

Results obtained from semen allergy prick test and in vitro IgE assay (ThermoFisher ImmunoCAP).

(\*Total IgE (reference range, 0.1–300kIU/L) for A: 3300, B: 200, C: 120, and D: 34.3).

For these reasons, a cut-off of 2 mm was clinically appropriate and, together with the suggestive history, indicated a high probability of HHS. Intradermal skin testing (IDT) has been shown to be more sensitive than skin prick testing for HHS in a small number of cases (Lee-Wong et al., 2008). We chose not to do IDT, because of the greater risks of anaphylaxis and because IDT can only be controlled for non-specific irritation by injecting a healthy volunteer with a patient's partner's semen. Similarly, the sIgE tests appear to have a sensitivity of only about 50% (Drouet et al., 1997) although this is hard to evaluate in a rare cases such as HHS. It is generally believed that the antigen(s) responsible for HHS are glycoproteins of prostatic origins (Weidinger et al., 2005). However, the true identity of the protein(s) remains unknown, and until they are identified, proper *in vitro* serological measurements of the allergens responsible for HHS will remain indistinct. As with previous studies (Bernstein, 2011), we found that there is often discordance between skin testing and serologic testing.

A history of atopy is associated with HHS (Bernstein, 2011) and from the clinical history of each patient; it was found that three of the women had allergies to other agents (Table 1). Patient D was highly atopic and was allergic to latex. She was advised to continue using latex-free condoms to avoid the risk of a severe reaction to both the semen and the latex. She was also informed that to avoid the risk of anaphylaxis she would be eligible for ART using her partner's washed spermatozoa if she decided against conceiving naturally.

In each case presented here, the semen was prepared using density gradient media and wash media routinely used in our IVF clinic. This sperm preparation protocol is used in ART, including IUIs. In a recent report, Frapsauce et al. described a case where a woman, previously diagnosed with HHS, experienced a severe allergic reaction during an IUI. The spermatozoa used were carefully washed, removing all the seminal plasma, and she was administered with antihistamine during the procedure (Frapsauce et al., 2010). There have also been reports of women developing a severe anaphylactic reaction to the components of the insemination media used during an IUI (Orta et al., 2003; Pagán et al., 2008). In the present study, it was demonstrated that spermatozoa separated from seminal plasma through density centrifugation and washed twice in media did not elicit an immune reaction in any of the women tested. Furthermore, the media used was negative in the SPT. Patients, who have severe HHS, with increased risk of anaphylaxis and show no reaction to washed spermatozoa, may undergo ART. We propose that an SPT be carried out in cases of HHS women who wish to conceive through ART. This test will alert the clinician of any potential adverse reactions, thus enabling proper management.

In addition to the immune reaction and associated physical discomfort, women with HHS experience emotional stress due to the impact it can have on

the relationship with her partner, and concerns about family planning. This was a concern shared by the women in each case. There are numerous published cases of successful pregnancies achieved naturally and through ART in women with HHS (Shah & Panjabi, 2004; Shapiro et al., 1981; Iwahashi et al., 1999; Resnick et al., 2004; Ferré-Ybarz et al., 2006). Moreover, one of our women, patient B, had successfully given birth to two healthy babies, conceived through IVF and naturally. We were able to reassure our patients that HHS does not cause infertility.

## Conclusion

This study has demonstrated that women presenting to the clinic with allergies to their partner's semen do not generate an immunoreaction to seminal fluid-free spermatozoa, nor to the components of the media used. This was reassuring to these patients, who had concerns about their fertility. In severe cases, where unprotected coitus can result in painful and, potentially, life-threatening reactions, ART is a feasible option. If there are no underlying female-factor fertility issues, or diminished sperm parameters (such as low motility or concentration), IUI is usually considered. Moreover, concerns regarding severe reactions during the IUI can be reduced by carrying out an SPT to the washed spermatozoa and the media prior to the IUI appointment.

Where ART is not required or not a feasible option, taking antihistamines just prior to any unprotected coitus is a suggested prophylactic treatment, and in severe cases, intravaginal or intradermal desensitisation may be discussed as a treatment option.

HHS is a relatively rare condition. However, it has been suggested that the incidence of human semen allergy is probably higher than reported because of lack of recognition in the medical community and underreporting by patients (Bernstein et al., 1997; Bernstein, 2011).

All of the women in this study were initially misdiagnosed, and HHS symptoms in all four cases presented here were abolished with condom use. HHS should therefore be considered a possible cause in women complaining of local and/or systemic symptoms after coitus, especially if the symptoms are not experienced with condom use.

Recognising this condition early will alleviate the stress and concerns that patients experience and enable clinicians to direct appropriate treatment.

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