

References

1. Turnbull AC, Anderson AB. Induction of labour. *J Obstet Gynaecol Br Commonw* 1968; 75: 32-41.
2. Steer PJ, Carter MC, Choong K, et al. A multicentre prospective randomized controlled trial of induction of labour with an automatic closed-loop feedback controlled oxytocin infusion system. *Br J Obstet Gynaecol* 1985; 92: 1127-1133.
3. Knutzen VK, Tanneberger U, Davey DA. Complications and outcome of induced labour. *S Afr Med J* 1977; 52: 482-485.
4. Fuchs AR, Fuchs F. Endocrinology of human parturition: a review. *Br J Obstet Gynaecol* 1984; 91: 948-967.
5. Saameli K. An indirect method for the estimation of oxytocin blood concentration and half-life in pregnant women near term. *Am J Obstet Gynecol* 1963; 85: 186-192.
6. Seitchik J, Amico J, Robinson AG, et al. Oxytocin augmentation of dysfunctional labour IV. Oxytocin pharmacokinetics. *Am J Obstet Gynecol* 1984; 150: 225-228.
7. Fuchs F. Cautions on using oxytocin for induction. *Contemp Obstet Gynaecol* 1985; 25: 13-16.
8. ACOG Technical Bulletin: Induction and augmentation of labour. No. 110, Nov 1987.
9. Brindley BA, Sokol RJ. Induction and augmentation of labour: Basis and methods for current practice. *Obstet Gynecol Surv* 1988; 43: 730-743.
10. Foster TCS, Jacobson JD, Valenzuela GJ. Oxytocin augmentation of labour. A comparison of 15 and 30 minute dose increment intervals. *Obstet Gynecol* 1988; 71: 147-149.
11. Blakemore KJ, Qin NG, Petrie RH, Paine LL. A prospective comparison of hourly and quarter hourly oxytocin dose increase intervals for the induction of labour at term. *Obstet Gynecol* 1990; 75: 757-761.
12. Sica Blanco Y, Sala NL. Oxytocin - Proceedings of an international symposium, Pergamon press, 1961; 127.

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Occasional Review

Allergy to Coitus

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Summary: Acute systemic hypersensitivity reactions to semen are rare but may be life-threatening. Chronic or recurrent local reactions are more common and may be misdiagnosed as infective or nonspecific vaginitis. The antigen(s) involved in these reactions reside in a glycoprotein fraction of seminal plasma. Allergic vulvovaginitis may also occur in sensitized women when they are exposed to exogenous allergens such as drugs, food and infective agents during sexual activity.

Skin testing and other relevant investigations are indicated when these disorders are suspected. Condom usage will prevent symptoms of coital allergy. Desensitization has had variable success in acute systemic hypersensitivity. Precoital antihistamines may modify local reactions.

It is clearly established that semen contains many antigens, both in the seminal plasma and on spermatozoa, that are capable of stimulating immunological responses in the female (1). The best characterized of these responses are those provoked by antigens of sperm and involve the development of antisperm antibodies both in blood and in genital tract secretions. Some of these antibodies are associated with infertility. Cell-mediated immunity (CMI) may also participate in sperm isoimmunization in the female.

It has also been known for some time that coitus can be complicated by other adverse immunological phenomena that are unrelated to sperm isoimmunity and

infertility. These include local and systemic hypersensitivity reactions to seminal antigens and abnormal defensive immunomodulation leading to recurrent vaginal infection. Vaginitis may also be induced by the seminal transfer of IgE antibodies from men who are sensitized to female vaginal secretions, microbes or other components or to semen. There is no evidence, however, that individuals with unexplained infertility have an underlying atopic diathesis (2).

This paper reviews the basis for and clinical implications of the various types of immunological reactions which mediate allergic reactions to semen.

ALLERGIC REACTIONS TO ANTIGENS IN SEMINAL PLASMA

Acute Systemic Hypersensitivity

The first clear description of a case of acute systemic hypersensitivity to semen was reported in the Dutch

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literature by Specken (3). This was preceded by an early intriguing report by James (4) of a pregnant woman who consistently experienced severe acute vomiting following intercourse and in whom semen skin-testing was positive and passive transfer reactions (Prausnitz-Kustner) could be achieved. Subsequently Halpern et al (5) reported a benchmark case of acute coital anaphylaxis associated with seminal plasma hypersensitivity. There have now been in excess of 30 case reports of acute hypersensitivity to semen with systemic features (6-30).

The recorded cases exhibited classical features of immediate generalized allergy. Typically, the patient may experience several or all of the following manifestations: local or generalized urticaria, orbital and vulval oedema, vulval and generalized pruritus, bronchospasm, lower abdominal pain, hypotension, and loss of consciousness. The onset of these symptoms may occur during coitus or within 15 minutes. They may reach their maximum intensity after 30 minutes and last for days, but usually abate after some hours in the absence of treatment.

The natural history of the syndrome is interesting. The patient will often have a personal or family history of atopy. She may experience mild local or systemic symptoms over a period of time (months or years) before progression to severe manifestations. Commonly, however, the onset of symptoms may occur during or following the first act of coitus, or they may appear following a change in coital, genital or reproductive circumstances. These include, for example, during and following a pregnancy, after gynaecological surgery or insertion of an intrauterine device, or after vasectomy or prostatectomy in the partner. These curious observations suggest an association with some perturbation of immunity in the female genital tract or some qualitative or quantitative alteration in the seminal immunogen (see below).

Provocation of the syndrome usually is not specific to a particular male partner and this is supported by immunological investigation of cases using semen from multiple donors. The condition is often self-limiting or fluctuating and may 'burn out' after several years, suggesting that natural desensitization may occur. On the other hand sexual abstinence or condom usage over a period of time may lead to a subsequent, temporary, abatement of symptoms.

One of the more bizarre reported cases of allergy to semen involved a pregnant woman who developed acute anaphylaxis following her third episode of coital exposure to canine semen over a 10-month period (6).

Local Reactions

Localized postcoital allergic seminal vulvovaginitis allergic reactions may coexist with the systemic syndrome (21) or may manifest as a specific chronically recurrent disorder. Chang (31) described 4 such cases of 'allergic seminal vulvovaginitis' in one family. The author has reported a further 4 cases (32) of this dis-

order which, by dint of the paucity of literature relating to its occurrence, might be thought to be rare, but may be a common, though unrecognized, clinical problem.

The clinical features of allergic seminal vulvovaginitis vary in type and severity but include local (vulval) pruritus, 'burning', swelling, erythema, and urticaria. Vulval vesicles may develop within hours and a thin watery vaginal discharge may ensue and last for several days.

Symptoms may commence during or immediately after coitus and often take up to a week to disappear. They may be modified in the acute phase by douching or vulval irrigation. The epidemiological and immunological associations of this phenomenon are similar to those of generalized hypersensitivity to semen and, as described above, there may be a strong familial tendency.

In clinical practice, it seems possible that mild local allergic reactions to semen may often be misdiagnosed as infective or 'nonspecific' vulvovaginitis. Such patients may have been labelled as having recurrent genital herpes, or may have been treated unsuccessfully for years for vaginal moniliasis, or other gynaecological disorders. The message, therefore, is clear, but not widely appreciated, that intractable vulvovaginitis with coitally-related manifestations, should be subjected to immunological investigation. Particularly suggestive features are a family history of atopy or of a similar genital condition, and the amelioration of symptoms by condom usage or abstinence.

Hypersensitivity to Exogenous Allergens in Semen

Exogenous allergens derived from drugs, food and other sources may be present in semen and thereby cause sensitization and hypersensitivity reactions in female partners. These may need careful investigation to differentiate them from reactions to intrinsic components of seminal plasma (see below). There have been case reports of coitally-related allergic reactions to thioridazine (a tranquilliser) (33), vinblastine (34) penicillin (35) and walnuts (36).

Allergic vaginitis may also be provoked by the inadvertent introduction into the vagina, by the fingers, of airborne allergens such as pollen, dust or animal hairs (37). Equally, vaginal exposure to chemicals in soaps, scented toilet tissues, sanitary napkins and contraceptive spermicides can elicit allergic responses in sensitized women.

It has also been proposed that the vaginitis in some women with genital candidiasis and other infections may be allergic in nature, with local IgE antibody production, and a secondary phenomenon of PGE₂ - induced suppression of cell-mediated immunity (38,39).

IMMUNOLOGICAL MECHANISMS

Acute generalized (systemic) allergy to semen, with or without a local component clearly represents a classical Type I (immediate, anaphylactic) hypersensitivity reaction. In this situation, the antigen reacts with

homocytotropic (reaginic) antibodies of the immunoglobulin E (IgE) class which are bound to mast cells or circulating basophils through a specialized region of the FC piece. This leads to degranulation of mast cells and release of vasoactive amines (e.g. histamine) which mediate the tissue and clinical features of anaphylaxis.

The basis of purely localized allergic reactions to seminal antigens is ill-defined. Reaginic antibodies presumably participate in the more acute cases but cell-mediated immunity (CMI) has also been implicated in recurrent allergic vulvovaginitis (21).

The Antigens

The antigens involved in these reactions are generally accepted to derive from seminal plasma. Isolated cases have been described in which humoral immunity or CMI to sperm has been detected, but this probably represents a casual rather than a causal association. Bernstein et al (21) described a unique case of coital allergy who had a positive skin test to sperm extract and antisperm IgE antibodies.

Seminal plasma is replete with potentially immunogenic molecules. Some of these are specific to semen but many others are common to other body fluids and tissues (40-42). These included serum, milk, saliva, sweat, nasal secretions, gastric fluid, urine, cervical mucus, uterine cervix, vagina, endometrium, Fallopian tube, ovary, liver and kidney. Also present in seminal plasma are protein and carbohydrate antigens derived from, or modified by, bacteria such as *B. proteus*, *B. subtilis*, *E. coli*, *S. faecalis* and haemolytic and non-haemolytic diphtheroids (43).

In addition, as described above, ubiquitous exogenous antigens may appear in semen, or be introduced into the vagina in other ways, and cause hypersensitivity reactions.

There is now, reasonably clear evidence that the antigen(s) involved in hypersensitivity reactions to semen itself are a heterogeneous family of glycoproteins with molecular weights lying between 10-30KD (5,7,10,14,15,18,23).

These molecules appear to be common to seminal plasma from all males, they are present in the semen of vasectomized men, and derive mainly, if not exclusively, from the prostate gland (17). They are probably species-restricted in view of the bizarre case described above (6) which exhibited hypersensitivity to canine but not human semen.

Prior sensitization to intrinsic seminal antigens might occur following repeated exposure to exogenous allergens of bacterial or other origin which exhibit common antigenic determinants.

Concurrent hypersensitivity to semen and sweat has been the subject of one case report (27).

The Immune Reactions

The reaginic nature of acute hypersensitivity to semen has been confirmed in many of the described cases by

the presence of specific IgE antibodies and by positive results from scratch and intradermal skin tests with whole seminal plasma or fractions thereof. Additional evidence has come from the *in-vitro* leucocyte histamine release assay and from *in-vivo* tests of passive transfer of hypersensitivity such as the Prausnitz-Kustner (P-K) reaction in human volunteers and passive cutaneous anaphylaxis (PCA) in nonhuman primates.

In those few cases where CMI has been implicated this has been delineated by *in-vitro* tests such as lymphocyte blastogenesis and leucocyte and macrophage migration inhibition in the presence of seminal plasma or its fractions.

It is intriguing to consider why overt allergic reactions are so uncommon given the potential for sensitization to 'foreign' antigens that is inherent in the coital act. The same question surrounds the incidence of isoimmunization against sperm antigens. The answer presumably relates to the complex homeostatic mechanisms which modulate immune recognition of seminal antigens in the female genital tract. As in any immunological response, genetic polymorphism must play a role; that is, the genetic predetermination of an individual to recognize and respond to specific antigen(s). A high degree of histocompatibility with their sexual partner has been reported in 2 of 4 women with semen allergy who were subjected to comprehensive Human Leucocyte Antigen (HLA) typing (21); the implication of this finding must however remain tenuous at present.

Of more importance are the established data concerning the immunosuppressive and immunomodulating activities of seminal plasma (44-46). Glycoproteins derived from murine, bovine and human seminal plasma are known to suppress lymphocyte blastogenesis induced by mitogens and specific antigens, and by allogenic cell-surface antigens in mixed lymphocyte reaction (MLR) experiments. Animal data also indicate that specific protein fractions of seminal plasma are synthesized at different locations in the male reproductive tract and that these fractions exert differential suppression of lymphocyte subpopulations. An additional local immunosuppressive effect may be mediated by PGE which is present in semen in concentrations capable of inhibiting *in-vitro* indices of CMI (47).

The clinical associations of some of the well documented cases of allergy to semen suggest that disruption of these homeostatic immune mechanisms may be important in pathogenesis. Thus, vasectomy, chronic disease or infection may impede the physiological immunosuppression of semen and pregnancy, infection or gynaecological surgery may alter normal immunomodulatory mechanisms in the female.

THE MANAGEMENT OF ALLERGY TO SEMEN

Whilst the clinical diagnosis of allergy to semen in its rare acute systemic form will be obvious to the most unprepared intellect, a heightened awareness of the possibility of local hypersensitivity is essential in the

differential diagnosis of atypical, recurrent and intractable forms of vulvovaginitis.

Investigation

Classical evidence of Type I hypersensitivity must be sought in skin tests using a 1:100 dilution of separated fresh seminal plasma. Donor semen may be used but for safety, aesthetic and logistic reasons it may be preferable to obtain a sample from the sexual partner. A positive scratch test will show an immediate wheal and flare reaction whereas in an intradermal test this reaction may take up to 20 minutes to develop. Higher dilutions of semen may be employed to quantitate a positive result.

This basic investigation is probably all that is necessary to make the diagnosis, which may however be supported by a raised serum IgE determination or by evidence of allergen-specific IgE in the radioallergosorbent test (RAST). The RAST is prone to vagaries but, when positive, provides significant evidence of specific hypersensitivity. The antigen (seminal plasma) is covalently coupled to methyl-cellulose discs which are then treated with the test subject's serum. The amount of specific IgE bound is estimated by the addition of radio-labelled anti-IgE.

Further investigational embellishments utilize the passive transfer of IgE antibodies such as in the P-K test whereby the patient's serum is injected into the skin of a normal recipient and the area is then challenged after 24 hours with seminal plasma. Needless to say the performance of tests in which biological fluids are injected into a recipient must be safeguarded by prior screening of their donor source for serological evidence of hepatitis B, syphilis and acquired immune deficiency syndrome (AIDS).

Clearly in the patient who exhibits other evidence of atopy to a putatively ubiquitous allergen comprehensive skin testing is appropriate in order to identify the provoking antigen to which she may be exposed in her partner's semen. However this is likely to be an extremely rare occurrence.

Tests for CMI to semen and more detailed evaluation of the nature of the seminal plasma antigen(s) in a particular case may be justified on a research basis but contribute little to the management.

Treatment

The treatment of acute systemic hypersensitivity to seminal plasma is a difficult problem. Abstinence is an effective but rarely acceptable solution. The use of a condom by the male partner is logical and equally effective but again may be unacceptable, particularly if procreation is planned by the couple. This particular requirement can be met by artificial insemination using sperm washed free of seminal plasma and preferably placed high in the uterine cavity using an 'embryo transfer' catheter.

As in other forms of atopy, desensitization has been attempted with variable success (5,20,23,24). In a patient with semen allergy, the desensitizing regimen should utilize at least, a partially purified, fraction of seminal plasma containing the relevant allergen(s) if any chance of success is to be anticipated. The maintenance of induced tolerance by regular coitus would also seem to be necessary to the success of immunotherapy.

Whilst prophylactic antihistamines are of no value in systemic hypersensitivity to semen, they may be quite effective in allergic seminal vulvovaginitis, particularly in mild cases. A recommended regimen is diphenhydramine hydrochloride (Benadryl) 50 mg orally taken 1 hour prior to planned coitus (31). A similar regimen using a nonsteroidal antiinflammatory agent may also be effective. Best et al (26) used mefenamic acid 500 mg 2 hours prior to coitus and every 4 hours afterwards as necessary with success in one patient. Some patients may also benefit from the use of intravaginal 8% cromolyn cream (48).

Condom or other therapy for local allergy may be suspended from time to time – say every 6 months – in an attempt to capitalize on the unpredictable natural history of the disease. Sometimes a period of treatment may be followed by an extended or permanent remission of symptoms.

References

1. Jones WR. The use of antibodies developed by infertile women to identify relevant antigens. In: Diczfalussy E ed. *Immunological Approaches to Fertility Control*. 7th Karolinska Symposium on Research Methods in Reproductive Endocrinology. Stockholm: Karolinska Institutet, Stockholm 1974. pp 376-404.
2. Harrison RF, Unwin A. Atopy in couples with unexplained infertility. *Br J Obstet Gynaecol* 1989; 96: 192-195.
3. Specken J.L.H. Een Merkwaardig geval van allergi in de gynaecologie. *Nederlands Tijdschrift voor verloskunde en Gynaecologie* 1958; 58: 314-318.
4. James DW. Pernicious vomiting of pregnancy due to sensitivity to semen. *West. J Surg Obstet Gynecol* 1945; 53: 380.
5. Halpern BN, Ky T, Robert B. Clinical and immunological study of an exceptional case of reaginic type sensitisation to human seminal fluid. *Immunol* 1967; 12: 247-257.
6. Holden TE, Sherline DM. Bestiality with sensitization and anaphylactic reaction. *Obstet Gynecol* 1973; 42: 138-140.
7. Levine BB, Siraganian RP, Schenkein I. Allergy to human seminal plasma. *N Eng J Med* 1973; 288: 894-896.
8. Frankland AW. Allergy: Immunity gone wrong. *Proc Roy Soc Med* 1973; 66: 365-368.
9. Frankland AW, Parish WE. Anaphylactic sensitivity to human seminal fluid. *Clin Allergy* 1974; 4: 249-253.
10. Schulz KH, Schirren C, Kueppers F. Allergy to seminal plasma. *N Eng J Med* 1974; 290: 916.
11. Berger H. Allergy to human semen. *NY State Med J* 1975; 75: 1072-1073.
12. Mikkelesen EJ, Henderson LL, Leiferman K, Gleich GJ. Allergy to human seminal fluid. *Ann Allergy* 1975; 34: 239-243.
13. Siraganian RP, Schenkein I, Levine BB. Immunologic studies of a patient with seminal plasma allergy. *Clin Immunol Immunopath* 1975; 4: 59-66.
14. Reunala T, Koshkimies AL, Bjorksten F, Janne J, Lassus A. Immunoglobulin E mediated severe allergy to human seminal plasma. *Fertil Steril* 1977; 28: 832-835.
15. Mumford DM, Haywood TJ, Daily LJ, McLerran CJ, McGovern JP. Female allergy to seminal plasma – a case report. *Ann Allergy* 1978; 40: 40-43.

16. Pevny I, Peter G, Schulze K. Sperm allergy of the anaphylactic type. *Der Hautarzt* 1978; 29: 525-530.
17. Voorhies R. Female allergy to seminal fluid. *Ann Allergy* 1978; 40: 252.
18. Kooistra JB, Yunginger JW, Santrach PJ, Clark JW. *In Vitro* studies of human seminal plasma allergy. *J Allerg Clin Immunol* 1980; 66: 148-154.
19. Kroon S. Allergy to human seminal plasma: a presentation of six cases. *Acta Dermat (Stockholm)* 1980; 60: 436-439.
20. Mathias CGT, Frick OL, Caldwell TM, Yunginger JW, Maibach HI. Immediate hypersensitivity to seminal fluid and atopic dermatitis. *Arch Dermatol* 1980; 116: 209-212.
21. Bernstein IL, Englander BE, Gallagher JS, Nathan P, Marcus ZH. Local and systemic hypersensitivity reactions to human seminal plasma. *Ann Int Med* 1981; 94: 459-465.
22. Shapiro SS, Kooistra JB, Schwartz D, Yunginger JW, Haning RV. Induction of pregnancy in a woman with seminal plasma allergy. *Fertil Steril* 1981; 36: 405-407.
23. Friedman SA, Bernstein IL, Enrione M, Marcus ZH. Successful long-term immunotherapy for human seminal plasma anaphylaxis. *JAMA* 1984; 251: 2684-2687.
24. Frisch C, Pujade-Laurance MD, Leynadier F, Dry J. Rush hyposensitisation for allergy to seminal plasma. *Lancet* 1984; 1: 1073-1074.
25. Wasson AW, Coy EA, Kooistra JB, Yunginger JW. Seminal plasma immunosuppressive factors in the spouse of a woman with seminal fluid allergy. *Am J Reprod Immunol Microbiol* 1987; 15: 99-100.
26. Best CL, Walters, Aldelman DC. Fixed cutaneous eruptions to seminal-plasma challenge: a case report. *Fertil Steril* 1988; 50: 532-534.
27. Freeman S. Woman allergic to husband's sweat and semen. *Cont Derm* 1986; 14: 110-112.
28. Shah A, Sethi S, Agarwal MK. Human seminal plasma allergy in India. *J Asthma* 1988; 25: 137-140.
29. Presti ME, Druce HM. Hypersensitivity reactions to human seminal plasma. *Ann Allergy* 1978; 63: 477-481.
30. Ohman JL, Malkiel S, Lewis S, Lorusso JR. Allergy to human seminal fluid: characterisation of the allergen and experience with immunotherapy. *J Allerg Clin Immunol* 1990; 85: 103-107.
31. Chang TW. Familial allergic seminal vulvovaginitis. *Am J Obstet Gynecol* 1976; 126: 442-444.
32. Jones WR, Gale AE. Concerning seminal plasma allergy. *Ann Allergy* 1978; 41: 325.
33. Sell MB. Sensitisation to thioridazine through sexual intercourse. *Am J. Psych* 1985; 142: 271-272.
34. Paladine WJ, Cunningham TJ, Donovan MA. Possible sensitivity to vinblastine in prostatic or seminal fluid. *N Engl J Med* 1975; 29: 52.
35. Green RL, Green MH. Postcoital urticaria in a penicillin-sensitive patient. *JAMA Assoc* 1985; 254: 531.
36. Haddad ZH. Food allergens. *Persp Allergy* 1978; 1: 2-3.
37. Berman BH. Seasonal allergic vulvovaginitis caused by pollen. *Ann Allergy* 1964; 22: 594-597.
38. Witkin SS. Immunology of recurrent vaginitis. *Am J Reprod Immunol Microbiol* 1987; 15: 34-37.
39. Witkin SS, Jeremias J, Ledger QJ. A localized vaginal allergic response in women with recurrent vaginitis. *J Allerg Clin Immunol* 1989; 81: 412-416.
40. Hekman A, Rumke P. The antigens of human seminal plasma: with special reference to lactoferrin as a spermatozoa-coating antigen. *Fertil Steril* 1969; 20: 312-323.
41. de Fazio SR, Ketchel MM. The occurrence of seminal plasma antigens in the tissues of women. *J Reprod Fertil* 1972; 30: 125-131.
42. Shulman S. Immunologic barriers to fertility. *Obstet Gynecol Surv* 1972; 27: 553-606.
43. Tung KSK, Cooke WD, McCarty TA, Robitaille J. Human sperm antigens and anti sperm antibodies II Age related incidence of antisperm antibodies. *Clin Exp Immunol* 1976; 25: 73-79.
44. Stites DP, Erickson RP. Suppressive effect of seminal plasma on lymphocyte activation. *Nature* 1975; 253: 727-729.
45. Hess EV, Marcus ZH. The inhibitors in seminal plasma. *J La Clin Med* 1980; 96: 577-581.
46. Anderson DJ, Tarter TH. Immunosuppressive effects of mouse seminal plasma components *in vitro* and *in vivo* *J Immunol* 1982; 96: 577-581.
47. Bygedeman M, Samuelsson B. Analysis of prostaglandins in human semen. Prostaglandins and related factors. *Clin Chim Acta* 1966; 13: 465-475.
48. Goldenhersh MH, Saxon A. Seminal fluid hypersensitivity (SFH): A new approach (Abstract). *Ann Allergy* 1989; 6: 256.