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Fertility and allergy: Is there a correlation?

Płodność i alergia – czy istnieje związek?

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Summary

Approximately 10% of couples have difficulties conceiving. Idiopathic infertility affects 10–15% of infertile couples. Some suspected causes of idiopathic infertility are lifestyle factors such as stress, diet, smoking, obesity, lack of physical exercise and alcohol consumption. At the same time, allergies and bronchial asthma are growing health problems in developed countries. Therefore, this study addresses the possible correlation between atopic diseases and fertility.

Several interesting cases of patients presenting symptoms of HSPH (*human seminal plasma hypersensitivity*) have been reported to date. In the majority of cases, allergy to semen is the IgE-dependent response to proteins contained in the seminal plasma. Observations indicating that patients presenting symptoms of HSPH are primarily allergic to allergens of dogs are particularly interesting. The structure of dog allergen Can f 5 is similar to the human PSA (55–60% similarity in the sequence of amino acids). This may explain the presence of IgE-dependent reactions following contact with semen during sexual intercourse in women allergic to dog fur.

This article presents the current state of knowledge on the phenomenon.

Keywords: **allergy • fertility • menstruation • canine allergy • IgE • cross-reactivity**

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INTRODUCTION

Infertility is one of the epidemics of the 21st century. Approximately 10% of couples have difficulties with conceiving. The aetiology of infertility is multiple. Some causes are known, e.g. absence of ovulation, obstruction of oviducts, the male factor, etc. There are also unknown causes of infertility, ones that are characterized by the inability to conceive without any detectable abnormalities in basic diagnostic investigations. Such cases are referred to as idiopathic infertility, which affects 10–15% of infertile couples. Some suspected causes of idiopathic infertility are lifestyle factors, such as stress, diet, smoking, obesity, lack of physical exercise and alcohol consumption. A correlation between infertility and endocrine, neurological and immunological disorders is also postulated [12, 13].

The correlation between allergic disorders and infertility still requires further examination, but on the basis of current evidence we can speculate that the link between them might be explained with several mechanisms: hypersensitivity to semen, persistent allergic inflammation of low intensity, hormonal changes or even the influence of treatment of allergic diseases.

This article presents the current state of knowledge on that phenomenon.

ATOPIC DISEASES AND SEX HORMONES

There is an increasing amount of evidence that sex hormones play a role in the intensity and severity of allergic reactions. The natural course of allergic diseases depends on many factors and sex is one of them. A number of interesting reports have been published so far on the impact of atopic diseases on the menstruation cycle in women [15, 38].

In childhood, boys are more predisposed to allergic diseases. However, with age the tendency becomes reversed. Bronchial asthma, food allergies and anaphylaxis are more common in women [20].

Atopic eczema in preschool children shows a slight male preponderance, depending on the study. In adults there are more females suffering from atopic eczema. Females report significantly more allergic reactions in questionnaire studies. The course of allergic diseases varies unpredictably during pregnancy, whereas hormone replacement therapy in postmenopausal women usually has a favorable influence on the course of asthma [10].

Anaphylaxis, acute systemic allergic reaction, may be life-threatening. In 2017 Turner P.J. et al. assessed the risk factors associated with fatal anaphylaxis, of which old age and co-morbidities were assessed to be particularly important. Yet, surprisingly, food allergies related to fatal anaphylaxis most commonly appears during the second and third decades of life. The risk factors for fatal venom anaphylaxis include middle age, male sex, white race, cardiovascular disease, and possibly mastocytosis [42].

In 2011 the results of the European Community Respiratory Health Survey II were published. The analysis based on the questionnaire responses of 3.354 participants of 27–57 years of age living in 21 countries demonstrated that early menarche was statistically more commonly associated with the subsequent development of bronchial asthma [2].

As asthmatics show changes in sex hormones such as a decrease in serum DHEA-S level regardless of drug therapy, they can also have associated menstrual irregularities [11].

In 2012 Galobardes et al. published The Glasgow Alumni Cohort Study, a report that included 3.502 women studied between 1948 and 1968. It was found that irregular menstruation was associated with the development of atopic bronchial asthma, but not of non-atopic bronchial asthma [15]. The study is consistent with Svanes et al.'s observations published already in 2005 and based on a survey among 8.588 women, as a part of the ECRHS I study (European Community Respiratory Health Survey), completed in Denmark, Iceland, Estonia, Norway and Sweden. The authors concluded that irregular menstruation in women between 26–42 years old were associated with the diagnosed bronchial asthma (OR 1.54 (95% CI 1.11 to 2.13)), symptoms of asthma (OR 1.47 (95% CI 1.16 to 1.86)), allergic rhinitis (OR 1.29 (95% CI 1.05 to 1.57)), bronchial asthma preceded by allergic rhinitis (OR 1.95 (95% CI 1.30 to 2.96)) [38]. In 2012 a retrospective study was published that analyzed medical files of 501 patients of the Yale University Hospital with laparoscopically confirmed endometriosis and 188 women with excluded endometriosis. A higher incidence of allergies in women with confirmed endometriosis was demonstrated, compared to women in whom endometriosis was excluded [28].

A very interesting study was published by Macsali F. et al. in 2009. This study investigated the correlation between the use of oral contraceptive pills (OCPs) and asthma using postal questionnaire in Denmark, Estonia, Iceland, Norway, and Sweden between 1999 and 2001. The gathered responses came from 5,791 women between 25 and 44 years old, of whom 961 (17%) used OCP. The use of oral contraceptive pills was linked with increased risk for asthma (odds ratio, 1.42; 95% CI, 1.09-1.86), asthma with hay fever (1.48; 1.08–2.03), wheeze with shortness of breath (1.27; 1.02–1.60), hay fever (1.25; 1.06–1.48), and >/=3 asthma symptoms (1.29; 1.05–1.58). These links/correlations were present among normal weight and overweight women [27].

The physiological role of hormones in a natural course of asthma is partially explained. In general, female sex hormones and their receptors favor asthma development [24]. Testosterone has an immunosuppressive effect and partially prevents immunoinflammatory processes

that triggers asthma. It contributes to the physiological balance by maintaining regulatory T cells [8, 24]. Laffont et al. have shown that in mice key regulators of type 2 inflammatory responses – group2 innate lymphoid cells (ILC2s) are greatly influenced by male sex hormones. Male mice have reduced numbers of ILC2 and their progenitors when compared to females. In response to environmental allergens, males exhibit reduced susceptibility to allergic airway inflammation. What is particularly interesting is that in mice orchiectomy, but not ovariectomy, abolishes the sex differences in ILC2 development [25].

DHEA, an androgen with a less virilizing effect, could be used as a treatment option for female-specific asthma [11]. DHEA reduced the steroid requirement without significant adverse reactions other than mild acne in patients with systemic lupus erythematosus [32]. Further examination of sex related asthma treatment is required [8, 11, 24].

ALLERGY AND FERTILITY

As stated above, sex hormones may influence the natural course of allergic diseases. However, do allergic diseases influence fertility? The answer to this question is still unclear, although there are several mechanisms in which allergic disorders may influence the chances of conceiving. Speculated causes of decreased fertility due to allergic disorders are presented in Table 1.

An interesting study concerning the links between infertility and allergies was published in 2016. The study enrolled 245 women (age 23–45) treated for infertility of unclear aetiology. Ninety-six of them had a past medical history of bronchial asthma. Patients were followed up for at least 12 months until pregnancy or discontinuation of observation. It was found that the probability of pregnancy was lower in women with bronchial asthma: the mean time to pregnancy in the case of women free from bronchial asthma was 32.3 months as opposed to 55.6 months in the case of women with medical history of this disease (bronchial asthma) (HR 0.5, 95% CI 0.34–0.74, p <0.001). Women burdened with bronchial asthma also demonstrated a lower ratio of successfully completed pregnancies (39.6% vs. 60.4%) [13].

The large cohort study completed in Denmark in 2014 involved the analysis of questionnaire data from 15.250 twins regarding the effect of bronchial asthma and allergy on fertility. In that group bronchial asthma was associated with a longer time to pregnancy: >1 year for 27% of asthma subjects compared to 21.6% of asthma-free ones. Those results were unchanged also after consideration of age, age at menarche, BMI and socio-economic status in the analysis [14].

In 2014 Juul Gade et al. published a report that attempted to indicate the reason for the negative effect of asthma on female fertility. The authors discussed some main theories regarding the causes of that unclear phenomenon. As a disease with an inflammatory background, bronchial asthma is a condition whose pathogenesis is associated with numerous mediators of inflammation. The disease may lead to mild generalized inflammation manifested by an increased activity of pro-inflammatory cytokines in peripheral blood (Il-6, TNF-α), which in turn promote neutrophils and NK cells. Moreover, both bronchial asthma and some gynaecological diseases may be associated with the metabolic syndrome. For example, polycystic ovary syndrome is common in overweight women and is a phenotype of obesity-associated bronchial asthma [21].

Another problem is the hypersensitivity reaction after contact with semen), which is diagnosed when local symptoms appear after contact with semen and are completely resolved when a condom is used. The symptoms can cause problems in conceiving due to the inability to have unprotected intercourse, but also due to allergic inflammation in the reproduction tract.

The paper by Jankowski et al. (2018) has shown that allergy symptoms after sexual intercourse may occur not only in women. Conducting their study using an Internet-based survey, the authors extracted a group of 52 patients with suspected allergy to uterine-cervical mucus and demonstrated that the secretion is a source of allergens, similarly to seminal plasma, but allergy is seldom diagnosed due to technical difficulties [19].

Another problem, albeit rare, is allergy to medication used in fertility procedures. A very intriguing case was reported in 2008 of anaphylaxis developed after an artificial insemination procedure in a 30-year-old woman. Skin tests were done in the patient indicating allergies to dust mites, cat, dog, horse, rabbit, grass, and also the medium used in the process of insemination. The applied medium (Upgraded B2 INRA medium; Labora-

Table 1. Current knowledge on reasons for decreased fertility in allergic disorders

Reasons for decreased fertility in allergic disorders
Persistent low-grade allergic inflammation
Allergy to semen (eg. cross-reactivity with Can f 5)
Symptoms after/during intercourse
Hypersensitivity to medication used during fertility procedures
Other, that require further research (Negative influence of allergen specific immunotherapy?)

tories CCD, Paris, France) contained BSA (bovine serum albumin), to which the patient was allergic and which caused symptoms of an anaphylactic reaction [30].

A different case was presented in a publication in 2018 by Gupta A. et al., in which a 27-year old patient with primary infertility was prepared for an in vitro procedure (frozen embryo transfer) with exogenous injectable natural micronized progesterone 100 mg (Hald; Intas). After injection, the patient developed burning and pain at the injection site associated with fever and breathlessness. Symptoms appeared the day following the administration of aqueous progesterone 25 mg (Pregcert AQ; Koye). Vaginal progesterone gel (Emprogest 8% w/w; Emcure) and 300 mg capsules (Hald; Intas) were tried with an effect of vaginal allergic inflammation. The fertility procedures were postponed due to the failure in progesterone administration. Luckily, the patient managed to conceive due to positive response to natural cycle modification and endogenous progesterone [18].

Theories on the influence of allergy on infertility that have been put forward to date require further research, such as the hypothesis that negative effect of allergy treatment, e.g. one of the effects of immunotherapy is lowering TH2 response and enhancing TH1 response, which would lower chances for embryoimplantation. EAACI position on immunotherapy clearly recommends that immunotherapy not be initiated during pregnancy. If it was initiated before conception it can be safelybe safely continued during pregnancy. There is no clear scientific data on problems with conceiving during immunotherapy [36]. Even in the case of venom immunotherapy used in patients with anaphylactic reactions in the past, on the basis of several case series it would seem that the procedure can be safely continued [31, 36]. Moreover, a striking case was published which has demonstrated a successful in vitro fertilization during venom immunotherapy [34]. Notwithstanding, eventual difficulties in conceiving during immunotherapy should be further analyzed.

In contrast to the above findings, Westergaard et al. pointed out that a successful pregnancy is associated with a strong skewing of the immune system towards a Th2-type immune response. Because such a deviation is also the hallmark of allergic disease, authors analyzed the reproductive history of 31.145 pregnant women who participated in a national birth cohort study in Denmark during September 1997 to March 2000. It was found that women, who had been trying tobecome pregnant for less than a year, more often had allergic rhinitis (OR = 1.18, 95% CI 1.06–1.32, P = 0.002) than women who had waited for more than a year. Early age at menarche was associated with an increased likelihood of allergic rhinitis. In general, atopy was not associated with an increased likelihood of successful outcome of pregnancies [45]. Tata et al. in a large primary-care data cohort of 491.516 women from the United Kingdom found no evidence that the fertility rates in women with asthma, eczema, or hay fever are lower than those of women in the general population [41].

In 1997 Nilsson et al. found that atopic mothers were more likely to have more than 1 child than non-atopic mothers [29].

This was not confirmed by Sunyer J. et al., who found that atopic women did not have a significantly higher fertility rate, but they may postpone having their first child compared with non-atopic women [37].

ALLERGY TO SEMEN

Several interesting cases of patients presenting symptoms of HSPH (human seminal plasma hypersensitivity) have been reported. In the majority of cases, allergy to semen is the IgE-dependent response to proteins contained in seminal plasma. It should be mentioned that local symptoms occurring after sexual intercourse may be associated not only with an allergy to the partner's semen, but also with hypersensitivity to latex, spermicides or moisturizing gels. Symptoms of HSPH may occur directly after intercourse or within one hour and involve pruritus, burning sensation, reddening and oedema of the vulva or other areas having contact with semen. Generalized reactions were also reported such as dyspnoea, symptoms of allergic rhinitis and conjunctivitis, generalized urticaria, exacerbation of atopic dermatitis, and also severe ones, including anaphylactic shock. Interestingly, HSPH is not associated with conceiving difficulties in all women [44].

Allergens of *seminal* plasma (*SP*) may be divided into SP-specific, mostly the human prostate-specific antigen (*PSA*) and non-specific, including drugs and food allergens, that accumulate in semen according to some authors [1].

Already in 2007 PSA was identified as a cause of anaphylactic reaction in a 38-year-old woman, whose symptoms developed directly after sexual intercourse. Immunoblotting SDS-PAGE with seminal plasma from the patient's husband with and without 2-mercaptoethanol was performed. The 28 kDa protein was identified to have been responsible for the development of symptoms. The protein turned out to be PSA [6].

Reports of cases of semen allergy are mostly based on casuistic reasoning. In 2012 Wolthers et al. published a case of a female patient with HSPH diagnosed at the age of 18 with a spontaneous remission of symptoms over the course of a 5-year follow-up [46].

The golden standard in the diagnosis of HSPH is the presence of symptoms after sexual intercourse and the complete disappearance of those symptoms after the introduction of condoms. Additional investigations such as skin prick tests and immunological tests with the partner's semen or with proteins obtained from semen are of supportive value. Those tests are usually positive in patients in whom generalized reactions are observed but may be negative in those whose reactions are local only [7].

In 2013 the case of a 37-year-old woman was published who had experienced pruritus of the vulva, oedema of pudendal lips and a strong discomfort in the abdomen for the previous 17 years after each contact with her husband's semen. The past medical history of the patient included positive skin prick tests on grass, trees, weeds and house dust mites. Her specific IgE for dog and cat was increased. Western blotting demonstrated binding of IgE specific for PSA in seminal plasma. Skin prick tests with native semen collected from her husband were done (after a previous confirmation that the husband was not a carrier of STDs). The results were positive. Twenty minutes after the test, the patient developed a generalized anaphylactic reaction. Desensitization with intravaginal method was applied using seminal plasma at dilutions of 1: 100,000; 1:10,000; 1:1,000; 1:100; 1:10; 1:1, administered every 30 minutes, with a satisfactory clinical outcome [3].

Although skin prick testing with semen are known to prove IgE dependent reaction, the methodology has a few drawbacks. An exceptionally interesting study on skin prick tests with seminal plasma was published in 2014. Tal Y. et al. suggested that the observed local reactions occurring after skin prick tests or intradermal tests with semen samples could be non-specific because of the presence of prostaglandins exerting a vasodilatory effect in semen. This was demonstrated by performing intradermal tests with diluted seminal plasma in two healthy volunteers and then re-testing after premedication with acetylsalicylic acid (ASA) at the dose of 1g for 7 days. Reduced skin reaction was observed after premedication with ASA that is an inhibitor of COX, and lead to reduced synthesis of prostaglandins and their reduced level in semen [39]. In fact, this research work can raise questions whether in some cases symptoms after intercourse in predisposed women are brought about with IgE dependent, allergic reaction, or are a non-immunological, hypersensitivity reaction to human prostaglandins. This problem requires further research.

Ghosh et al. analyzed the immunological response in 2 female patients with confirmed HSPH after the end of the specific immunotherapy with PSA. They confirmed a shift of the Th1/Th2 balance towards Th1 [16]. That result confirms the potential effectiveness of immunotherapy in patients with HSPA.

In 2013 Tan and Bernstein published a report of their study of 12 female patients in Cincinnati, Ohio diagnosed with hypersensitivity to semen and treated with intravaginal desensitization with diluted semen from their partners. The follow-up study included phone interviews. The results have shown that in the study group, most women gave birth without complications and on time, two could not get pregnant, and two were not interested in getting pregnant. Interestingly, the efficacy of the applied immunotherapy had no effect on the ability to conceive [40].

In 2011 Song et al. published a report regarding a 33-year-old woman with a past medical history of bronchial asthma, allergic rhinitis and atopic dermatitis, who complained about skin changes occurring after sexual intercourses with her husband. The patient gave birth six months before and she had had no previous pathological symptoms after sexual intercourses. Skin prick tests with seminal plasma were done and confirmed hypersensitivity of allergic type. The use of condoms completely eliminated the symptoms. Considering the fact that the patient wanted to get pregnant again, it was recommended that she use Loratadine at a dose of 10 mg an hour before sexual intercourse. The therapy proved successful. The patient got pregnant and gave birth to a healthy child [35].

Despite extensive research discussed above, the actual influence of HSPH on human fertility requires further research.

CROSS-ALLERGY BETWEEN CAN F 5 AND HUMAN PSA

Observations indicating that there is a group of patients who present symptoms of HSPH due to an allergy to dogs have also been published. Canine allergen extract contains several proteins possessing allergenic properties. Some well-characterized canine allergens are the following:

- Can f 1, Can f 2, Can f 4, Can f 6 – lipocalins, present in hair, fur and saliva. Can f 1 is the main allergen considered to be the most important canine antigen. 75% of patients allergic to dogs have allergenically specific IgE against Can f 1. Can f 1 and Can f 2 have the same epitopes [23].
- Can f 3 – dog serum albumin (DSA) – is an approx. 70 kDa protein. Its presence was demonstrated in blood plasma, saliva, fur and epithelium. The protein is synthesized in salivary glands and the liver [23]. The prevalence of allergy to Can f 3 is different in various populations and is estimated at 35–48% for the total population of people allergic to dogs.
- Can f 5 – prostatic kallikrein, also known as arginine esterase, is a 28 kDa protein present in dog urine and fur [4].

The latter allergen is particularly interesting in the context of the correlation between allergy and fertility disorders. Similarly to the prostate-specific antigen (PSA) in humans, the protein is secreted from prostate under the influence of androgens. This suggests that in the case of an allergy to Can f 5, symptoms appear only after contact with male dogs [33]. It was demonstrated that castration leads to a drastic reduction of the level of Can f 5 in dog's urine and fur [9]. Taking into consideration the fact that in some regions dog castration is common but rare in other regions, the allergic profile of patients may be significantly different in different populations. Can f 5 is the main allergen, binding to asIgE in 70% of dog-allergic patients. 30% of patients are allergic only to Can f 5, and in that group we expect some significant differences in

the development of clinical symptoms after contact with male and female dogs [41]. The structure of Can f 5 is similar to the human PSA (55–60% similarity in the sequence of amino acids). That may explain the presence of IgE-dependent reactions following contact with semen during sexual intercourse in women allergic to dog fur [9].

The allergy to Can f 5 seems to be an increasing problem. In 2016 Ukleja-Sokolowska N. et al. published results of their study involving the analysis of the immunological profile of 70 patients allergic to dogs or cats. In the analyzed population, the allergy to Can f 5 was confirmed in 22 patients (31.4%). IgE specific for Can f 1, Can f 2, and Can f 3 were found in 28 (40%), 10 (14.3%), and 16 (22.9 %) patients, respectively [43].

In 2017 Basagaña et al. published a report analyzing the results of immunological tests in 70 patients with a confirmed allergy to canine antigens. It turned out that in the study group the increased level of IgE specific for Can f 5 occurred in as many as 47 patients (67%). IgE specific for Can f 1, Can f 2, and Can f 3 were found in 29 (41.4%), 10 (14.3%), and 14 (20%) patients, respectively. Moreover, as much as 37% of patients were allergic only to Can f 5 [5].

In their recent study published in 2018, González-de-Olano et al. examined 27 women allergic to dogs. The allergy was confirmed by clinical symptoms and a positive result of skin prick tests. In the study population, the main allergen turned out to be Can f 5, to which 22 of 27 patients were allergic (81.4%). Interestingly, 4 subjects in the study group had symptoms occurring after a sexual intercourse, associated with the cross-allergy to PSA from semen (18.1%) [17].

What is interesting, in recent study by Keck et al. monosensitisation to Can f 5 was associated to negative nasal provocation test in children [22].

Allergy to Can f 5 may be currently diagnosed exclusively on the basis of allergenic components, both using the quantitative method, assessing the level of specific IgE (ImmunoCap), and the semi-quantitative method with available multiplex platforms (ImmunoCap ISAC, ALEX). Considering a relatively low availability of those diagnostic methods and their high cost, the majority of people allergic to dogs do not know their allergenic profile. Yet, knowledge of the profile has some practical aspects, including consideration of owning a female dog by patients with an isolated allergy to Can f 5, a potential lack of efficacy of specific allergen therapy for canine allergens due to a low content of Can f 5 in the extract, and also a possible cross-reaction with human PSA and associated consequences [26].

Inevitably, further studies are necessary in order to demonstrate all clinical aspects of the allergy to Can f 5, particularly in the context of its clinical significance for women experiencing difficulties with conceiving. The problem raises several questions. Do women allergic to Can f 5 experience symptoms of HSPS? Is there any kind of allergic inflammation in their reproductive tract that can compromise their ability to get pregnant? How strong is cross reactivity between PSA and Can f 5? Those questions require further examination.

CONCLUSION

The correlation between atopic diseases and fertility remains unclear. Numerous studies confirm that the risk of problems with conceiving is higher in people burdened with atopy, compared to the healthy population. Undoubtedly, immunological disorders constituting a basis for allergic diseases may influence the hormonal metabolism. In addition, the assumptions of cross-allergy between semen and allergens of fur animals are very intriguing. However, further research is necessary to assess the clinical significance of that phenomenon.

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