


Abnormal sperm morphology is associated with sensitization to inhaled allergens

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Abstract

Background: Allergy is associated with the loss of tolerance of environmental antigens, combined with a pathological immune response. There were no studies up to date that would show whether the quality of semen decreases in people with allergic diseases. **Material and methods:** The research included men who reported to the Gynecological Outpatient Clinic due to reproductive difficulties, defined as the lack of pregnancy after one year of regular intercourse. Semen quality was assessed according to the World Health Organization (WHO) standard. All patients underwent skin prick tests with the most important inhalation allergens (such as hazel, silver birch, mugwort, rye, dog, cat, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, alder, *Alternaria alternata*, *Cladosporium herbarum*, and grass mix). The data was statistically analyzed. **Results:** Results of 52 patients aged 25–52 years (34.62 ± 4.96) were analyzed. The mean BMI (Body mass index) was 28.25 (+ –3.77). It was found that 38 men (73%) had increased body weight, and 14 men (26.9%) were obese (BMI ≥ 30). 13 patients were smokers (25%), and 24 patients (46%) had skin tests positive for at least one inhaled allergen. Sperm tail defects were statistically more significant in patients allergic to birch, rye, cat, alder, and grass. In patients allergic to *Alternaria alternata*, head defects were statistically more significant ($p < .05$). No association was found between allergy to house dust mites, mugwort, hazel, and dogs and the deterioration of semen. **Conclusion:** Allergy due to inhalation allergens had an influence on the quality of male semen. Further research is necessary to establish the immunological bases of this phenomenon.

Keywords

reproduction, semen, allergy, fertility, allergens

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Introduction

Over the past 50 years, the quality of semen in men of reproductive ages has declined sharply. The key to fertilization is when a spermatozoid can travel from the testicles to the fallopian tube. This process is controlled by extra and intracellular factors, which also play a key role in the regulation of sperm motility and during the process of chemotaxis.¹

It is very important to analyze the causes of deterioration of male semen. Etiology of this process takes into account environmental pollution, smoking, age, and all the accompanying diseases. Obesity is also an increasing issue. It

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is worth noting that in the last 50 years, there has been a dramatic increase in the incidence of allergic diseases in the population of developed countries. In fact, allergy is associated with the loss of tolerance of environmental antigens, associated with a pathological immune response.² There were no studies that would show whether the quality of semen decreases in people with allergic diseases.

The aim of this research is to compare the sperm parameters in patients with and without sensitization to common inhaled allergens. The data underwent statistical analysis to establish if there is an association between allergy and the quality of sperm.

Material and methods

The study included men who reported to the Gynecological Outpatient Clinic due to reproductive difficulties, defined as the lack of pregnancy in a relationship after one year of regular intercourse. All patients went through detailed medical interview and physical examination, including examination of the prostate and external genitalia.

Exclusion criteria were as follows:

1. Serious, chronic diseases and patients on medication that could impact the results of this study.
2. Past surgery concerning testicles in the medical interview.
3. Problems with sexual function in the interview (e.g., difficulty with ejaculation or small volumes of fluid ejaculated, erectile dysfunction).
4. Abnormalities in the examination of the testicle area (pain, swelling, or a lump in the area, varicocele).
5. Signs of a chromosomal or hormonal abnormality in physical examination (gynecomastia, decreased facial or body hair, or other).
6. Ongoing or completed allergen-specific immunotherapy.

This cross-sectional study took place between August 2018 and December 2019. The size of the study population was established prior to conducting the study and was based on previous studies concerning allergen profile of patients allergic to canine and inhaled allergy, as well as different causes of deteriorated semen parameters. Another factor taken into account when establishing the size of population was the financial support received for the research.^{3,4}

Patients who met the criteria were qualified for the study so as to report to the Clinic. Detailed medical history and environmental history were gathered, and all the patients underwent a physical examination. Their heights and weights were measured. The semen quality was assessed in the participants' partners according to the WHO standard of seminology assessment, using the computer-assisted semen analysis (CASA). Biological materials were submitted for analysis immediately

after its receipt by masturbation. Moreover, skin prick tests with inhalation allergens were also performed in all the patients using the HAL kit (including positive control, negative control, hazel, silver birch, mugwort, rye, dog, cat, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, alder, *Alternaria alternata*, *Cladosporium herbarum*, and grass mix). Skin prick tests were considered to be positive if the mean diameter of the resulting blister was 3 mm, with normal skin reactivity (histamine \geq 3 mm, negative control negative), which is the most commonly used method.^{5,6}

A permission was obtained from the Committee of Bioethics no. KB 432/2018 to carry out the study. The study was funded by the Statuary Activity of the L. Rydygier Collegium Medicum, Nicolaus Copernicus University, WL-121. The authors declare no conflict of interests in regards to this research.

All patients submitted their written informed consents on the participation in the study.

Statistical analysis was performed with the help of Microsoft Excel 365 and R software, version 4.0.3. Comparison of values of quantitative variables between two groups was performed using the Mann–Whitney U test. Correlations between quantitative variables were analyzed using the Spearman's correlation coefficient. A significance level of 0.05 was adopted in the analysis. Thus, all *p* values below .05 were interpreted as showing significant relationships.

Results

Results of 52 patients aged 25–52 years (34.62 ± 4.96) were analyzed. The mean BMI was $28.25 (+3.77)$. It was found that 38 men (73%) had increased body weight, and 14 men (26.9%) were obese (BMI > 30). 13 patients were smokers (25%). The patients donated 0.5–9 ml of semen for the study. The evaluation of semen parameters is presented in [Table 1](#).

It was found that in the studied population, age correlated significantly ($p < .05$) and positively ($r > 0$) with the semen leukocyte count and with the presence of immobile and abnormal spermatozooids. Moreover, age correlated significantly ($p < .05$) and negatively ($r < 0$) with parameters such as progressive movement and normal spermatozooids. In general, the older the age, the worse were the semen parameters in the study population. Results of the analysis are presented in [Table 2](#).

No correlation was demonstrated between male body weight, BMI, and semen quality ($p > .05$).

Smoking had a statistically significant ($p < .05$) effect on the Teratozoospermia index ([Figure 1](#)). No statistically significant influence was found on the remaining semen parameters.

In the study population, 24 patients (46%) had positive skin tests for at least one inhaled allergen. The number of patients with positive skin tests for individual allergens is shown in [Figure 2](#).

Table 1. Semiogram of patients, with the analysis of abnormalities.

Assessed parameter	Mean	SD	Median	Min	Max	Q1	Q3
No. of round cells (M/mL)	1.83	1.22	1.5	0.2	5.9	1	2.2
Leukocyte count (M/mL)	0.24	0.2	0.2	0	0.9	0.1	0.3
Concentration (M/mL)	73.47	91.25	43.9	1	389.9	9.45	92.1
Total count in ejaculate (M)	260.35	328.76	152.25	1	1370.6	40.75	329.83
Viability (%)	56.84	15.78	56.5	21	87	46.25	67.5
Progressive movement (%)	30.57	17.54	28	1	70	15	45.5
Non-progressive movement (%)	9.33	3.69	9	0	19	7	10.75
Immobile (%)	60.26	17.61	63	24	92	46.5	73
Normal spermatozooids	7.2	4	6.5	0	18	5	10
Abnormal spermatozooids	92.98	3.86	94	82	100	90	95
Defects of the head	88.8	5.15	89	78	99	86	92
Defects of the midpiece	28.37	11.27	27	9	52	19	35
Defects of the tail	8.93	11.82	5	0	62	2	11
Cytoplasm drops	0.38	0.88	0	0	5	0	0.75
Teratozoospermia index	1.37	0.16	1.3	1.1	1.7	1.3	1.5

Table 2. Relationship between age and semen condition.

Semiogram	Age
	Spearman correlation coefficient
No. of round cells (M/mL)	$r = 0.166. p = .274$
Leukocyte count (M/mL)	$r = 0.352. p = .012^*$
Concentration (M/mL)	$r = 0. p = .998$
Total count in ejaculate (M)	$r = 0.02. p = .89$
Viability (%)	$r = -0.033. p = .836$
Progressive movement (%)	$r = -0.369. p = .011^*$
Non-progressive movement (%)	$r = -0.028. p = .853$
Immobile (%)	$r = 0.354. p = .015^*$
Normal spermatozooids	$r = -0.312. p = .035^*$
Abnormal spermatozooids	$r = 0.301. p = .045^*$
Defects of the head	$r = 0.155. p = .335$
Defects of the midpiece	$r = 0.043. p = .788$
Defects of the tail	$r = 0.161. p = .315$
Cytoplasm drops	$r = 0.015. p = .923$
Teratozoospermia index	$r = 0.113. p = .487$

The effect of the presence of allergy to at least one inhaled allergen on semen quality was analyzed and no relationship was found. The situation was slightly different in the case of the analysis of allergy to individual allergens. It turned out that sperm tail defects were statistically more significant in patients allergic to birch, rye, cat, alder, and grass ($p < .05$)—Figure 3. In patients allergic to *Alternaria alternata*, head defects were statistically more significant ($p < .05$). However, no association was found between allergy to house dust mites, mugwort, hazel, and dogs and the deterioration of semen.

Discussion

In developed countries, 14% of couples have difficulties related to pregnancy.⁷ Male infertility occurs in approximately 40% of the cases.⁸

A number of causes are considered to contribute in the deterioration of the semen quality. The influence of environmental pollution, sedentary lifestyle, the influence of mobile phones, obesity, smoking, and many other factors are taken into account.^{9–11}

Overweight and obesity are a growing problem in the general population. According to the epidemiological study

completed in 2013, these complications affect about 36.9% of men. This is a significant increase since 1980, when BMI > 25 was found to be 28.8%.¹² Shayeb AG et al. found that obese men had a lower volume of semen, but the semen parameters were normal.¹³ In the study by Belloc S. et al., conducted from 2010 to 2011 on a large population of 10,665 men, it was found that increased BMI had an impact on reduced sperm quality, volume, concentration, and mobility. It had no effect on the number of normal spermatozooids.¹⁴ In 2010 and 2013, two meta-analyses were published, the conclusions of which were contradictory. Sermondade et al. found that obesity increased the risk of abnormal sperm count.¹⁵ However, in a study by MacDonald et al., no relationship was found between BMI and semen quality.¹⁶ Our research did not confirm the existence of a relationship between being overweight and obese and

semen quality. At the same time, there were a significant percentage of overweight and obese men in the study population.

Smoking is a recognized factor deteriorating semen quality. The meta-analysis published in 2016, based on the analysis of 5865 cases of men, indicated that smoking reduced the number of spermatozooids and their viability.¹⁷ Asare-Anane H. came to similar conclusions, indicating a significantly lower semen volume, spermatozoid concentration, motility, and total count.¹⁸ In our study, smoking had a statistically significant ($p < .05$) effect only on the Teratozoospermia index.

Another important parameter taken into account in our analysis was the age of the patients. It was found that with age, semen parameters deteriorated, including an increase in the presence of immobile and abnormal spermatozooids, as well as a decrease in the progressive movement and the count of normal spermatozooids. During the research of Li WN. et al. in 2019, which included an analysis of 71,623 infertile men who were diagnosed at the Reproductive and Genetic Hospital in Hunan, China between 2011 and 2017, it was found that various semen parameters decreased with the age of patients, and that the concentration and motility of spermatozooids were the best predictor of fertility.¹⁹ In a 2018 study from Hong Kong, it was found that age ≥ 40 years is negatively correlated with the volume of semen and the progressive movement of spermatozooids.²⁰

It is interesting to analyze the influence of atopic diseases on semen quality. The incidence of these diseases is increasing in Poland. There are many reports of the development of post-coital symptoms in women with atopic diseases. Hypersensitivity to semen, manifested by symptoms developing after sexual intercourse, was already described in the 1970s.²¹ Symptoms of semen hypersensitivity in women may take the form of local reactions as

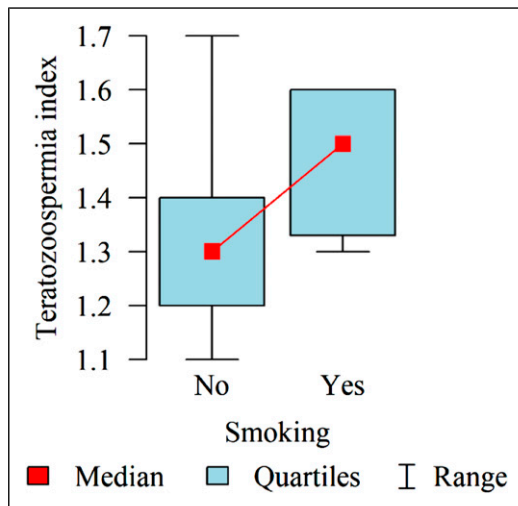


Figure 1. Smoking and teratozoospermia index.

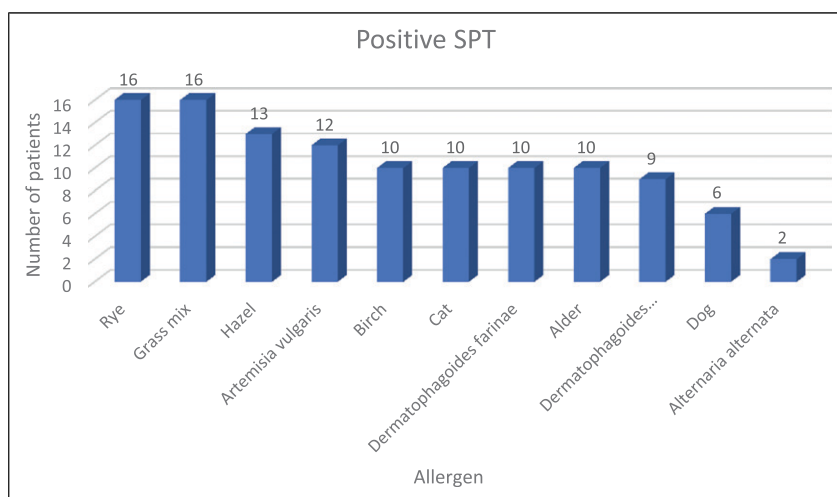


Figure 2. Distribution of positive skin tests for individual allergens in the studied population.

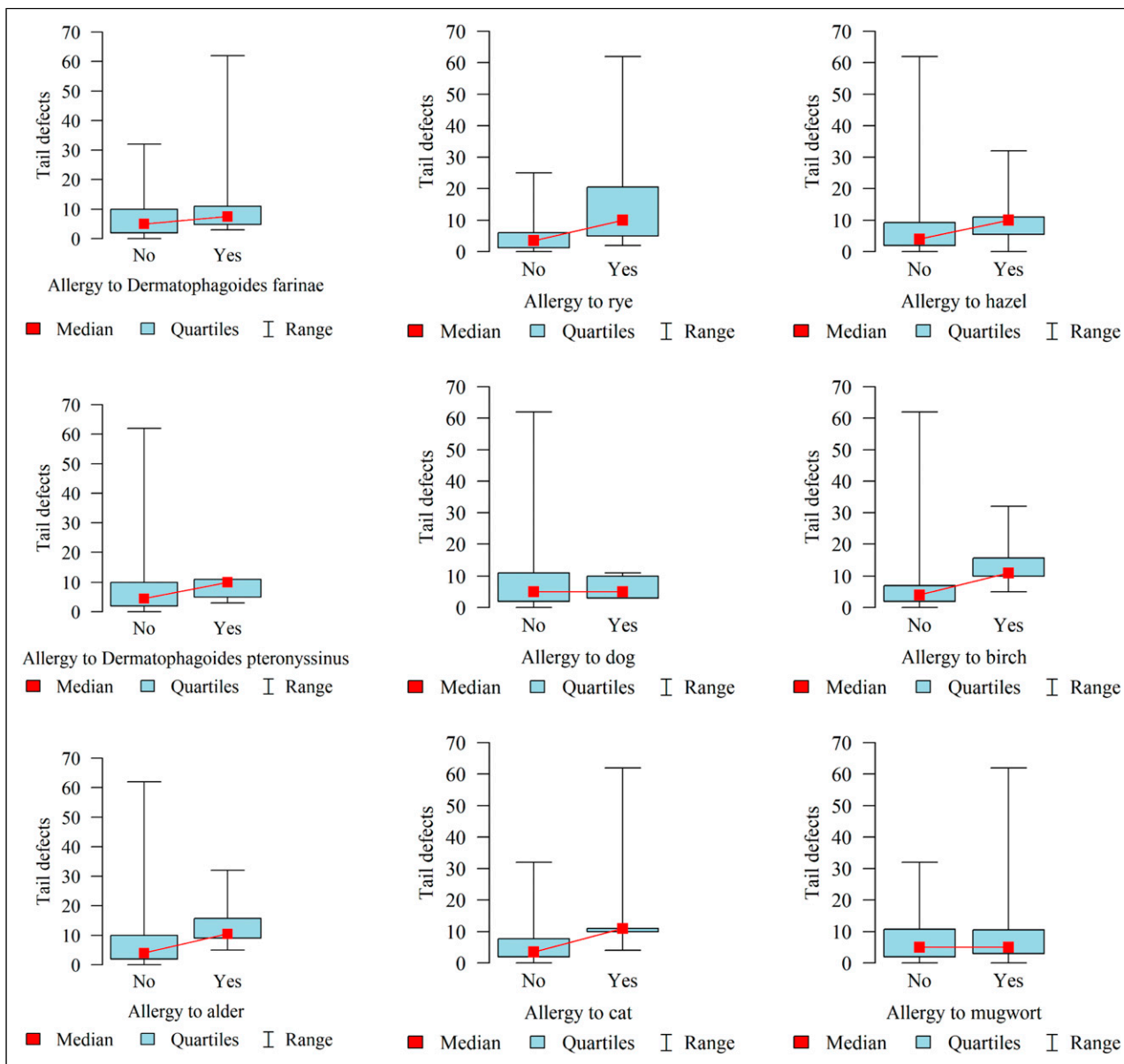


Figure 3. Occurrence of sperm tail defects in patients allergic to individual allergens.

well as severe generalized reactions (*human seminal plasma anaphylaxis—HSPA*).^{22,23} An interesting issue is the reported cross-allergy, which occurs in patients who are allergic to dogs. Can f 5, a prostate kallikrein, which is structurally related to human prostate-specific antigen (PSA), is the major allergen among canine antigens that are potentially sensitizing in women.^{24,25} Esfandiari et al. found that the prevalence of allergy among female patients seeking infertility treatment is high compared to the general population (54,7% vs 10–30%). However, allergy was not found to be associated with in vitro fertilization (IVF) cycle outcomes.²⁶

The way atopic diseases influence infertility may have different etiopathogenesis. It might be gathered with low

grade systemic inflammation, influence of medication used to treat allergies, hypersensitivity to fertility treatment, and possibly other factors as well.²⁷

There are studies showing it is likely that systemic inflammation found in asthma patients also affects the uterine mucosal layer and impairs effective implantation of the embryo. Inflammatory cells play an important role in reproductive health during pregnancy. However, controlled asthma may be associated with a reduced risk of infertility, even if the exact mechanism remains unclear.^{28,29} An interesting case report was published on two women, who were able to conceive naturally after starting mepolizumab treatment for severe eosinophilic asthma. Although in

general, mepolizumab is contraindicated in pregnancy due to lack of safety data, it is possible that unexplained infertility in people with severe eosinophilic asthma may be corrected by mepolizumab treatment, or effective asthma treatment in general.³⁰

One interesting subject is the use of medication on male fertility. Histamine receptors (HRH1, HRH2, and HRH4) have been described in Leydig cells of different species, including human. Furthermore, HRH1 and HRH2 receptors are present in peritubular and germ cells, and HRH2 antagonists have been found to negatively affect peritubular cells and reduce sperm viability. Testicular mast cells are the major source of locally produced histamine. It should then be considered that anti-histamines may affect testicular homeostasis by increasing or decreasing steroid production.³¹ Anti-histamines are widely used in most allergic diseases and are available OTC in many countries. Additional data on a large population are required to show the real-life influence of long-term anti-histamine treatment on sperm parameters.

In dermatology, the negative effect of treatment of common conditions on male fertility is well recognized. Administration of methotrexate and finasteride has resulted in severe oligospermia and reversible infertility. Ketoconazole has had negative effects on sperm motility and testosterone production. There are also some limited data on negative effects of tetracyclines, erythromycin, chloroquine, glucocorticoids, spironolactone, and antihistamines on fertility.³²

The association of fertility with other atopic diseases is less recognized. In 2020, Napolitano et al. published an interesting systematic review of the influence of treatment on fertility in atopic dermatitis (AD) patients.²⁸ The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity. Baricitinib in a dose high above registered for humans has shown to reduce fertility, have a teratogenic effect, reduce bone growth and fetal weight in the uterus, and increase embryoletality in a murine model.³³ The impact of new systemic, biological medications (Dupilumab, Lebrikizumab, and Fezakinumab) for AD on future fertility is largely unknown. In most cases, animal models have shown no negative effect, but it does not exclude an adverse impact on human gametes or reproduction.²⁸

It is worth noting that basic semen parameters, sperm functions, and DNA integrity may be affected by chronic inflammation of the male genital tract. Adequate management of affected patients appears mandatory, but low-dose corticosteroids, used also in allergic disorders, can be considered as one of the therapeutic options.³⁴

As per our knowledge, the current study is the first in trying to answer the question whether the presence of atopic diseases has an impact on the quality of semen. In 2009, Allam JP analyzed the influence of mast cells—key

cells in the development of allergic reaction symptoms—on sperm quality. The researchers found no correlation between a higher concentration of mast cells and significant semen parameters.³⁵

In the group of patients we studied, sperm tail defects were more common in patients allergic to birch, rye, cat, alder, and grass. Head defects were found to be significantly more frequent in patients allergic to *Alternaria alternata*. This observation certainly requires further research. It can be hypothetically assumed that a chronic inflammation associated with an allergic disease affects semen quality. It is known that the semen of healthy men contains numerous interleukins, including cytokines responsible for the Th2 response, such as IL 10 and IL 13.³⁶ The response dependent on pro-inflammatory cytokines (IL-17, IL-6, IL-18, and IL-12) and related to corresponding Th (IFN- γ , IL-4, IL-10, and IL-13) underlies atopic diseases.³⁷

Risk factors for allergic diseases and fertility problems may be similar to some extent. Environmental pollution is a frequently described etiological factor for atopic diseases.³⁸ Environmental contamination is also one of the factors that can potentially reduce the quality of semen.^{39,40} Unfortunately, the qualitative and quantitative differentiation of particles that create environmental pollution make it difficult to compare reports published so far and draw final conclusions.⁴¹

Limitations of this study include relatively small patients' population. An interesting approach would be to widen allergy diagnosis, for instance, using molecular in vitro methods to find an association between specific allergen components sensitization and sperm parameters. Some defects could be gathered with direct influence of specific IgE or IgG due to cross-reactivity. There is scarce data on this subject, although were reports on antigenic cross-reactivity between the venom allergen (antigen 5) and mammalian testis proteins, which did not possess a high risk to develop autoantibodies, leading to infertility.⁴² Another limitation of the study is the lack of detailed examination of other causes of male infertility, including hormonal and immunological profile, and karyotype assessment. Exclusion criteria were based on the interview and medical history, followed by careful physical examination (which included genital area assessment). Further in-depth studies are required to examine other possible pathomechanisms behind the observed sperm defects, on a large population of patients.

Conclusion

There is no doubt that the development of civilization has brought about some changes in our living environment, diet, and lifestyle of far-reaching consequences. Amongst them, there is certainly an increase in the frequency of

atopic diseases and the growing problem of infertility. Finding associations among the factors causing the above-mentioned abnormalities may help to understand better the natural course of these diseases.²⁷

In our research, we found an association between sperm tail defects and allergy to birch, rye, cat, alder, and grass. Head defects were found to be significantly more frequent in patients allergic to *Alternaria alternata*. Those results, however interesting, require further analyses. Studies, based on a larger population, are needed to confirm the relationship between atopic diseases and semen quality.

Declaration of conflicting interests

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Ethics approval

Ethical approval for this study was obtained from Collegium Medicum in Bydgoszcz, NCUCommittee of Bioethics KB 432/2018.

Informed consent

Written informed consent was obtained from all subjects before the study.

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