

# Correlation of leukocytospermia with clinical infection and the positive effect of antiinflammatory treatment on semen quality

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**Objective:** To investigate the correlation between leukocytospermia, bacteriospermia, and clinical signs of infection and to evaluate antiinflammatory therapy.

**Design:** Prospective nonrandomized study.

**Setting:** Andrologic clinic at university hospital.

**Patient(s):** A total of 56 patients were evaluated, and 12 of them received further treatment with a Cox-2 inhibitor.

**Intervention(s):** Semen analysis and clinical investigation were done according to World Health Organization guidelines. Serum levels of leukocytes, C-reactive protein (CRP), and prostate-specific antigen (PSA) were measured from blood samples.

**Main Outcome Measure(s):** Sperm concentration, leukocyte concentration, serum leukocyte count, CRP, PSA, bacterial growth.

**Result(s):** Leukocytospermia ( $>1 \times 10^6/\text{mL}$ ) was present in 60.7% of the semen samples, significant pathogenic bacterial growth was detectable in 35.7%, and 14.3% of the samples fulfilled the criteria for ejaculate signs of infection. All serum parameters were within the normal range. In abacterial leukocytospermia, treatment with a Cox-2 inhibitor decreased leukocytospermia from  $5.5 \times 10^6/\text{mL}$  to  $1.0 \times 10^6/\text{mL}$  ( $P=.001$ ) and increased sperm concentration from  $22.5 \times 10^6/\text{mL}$  to  $48.0 \times 10^6/\text{mL}$  ( $P=.02$ ).

**Conclusion(s):** There was no evidence of an immune response in the peripheral blood system. In abacterial leukocytospermia, treatment with a Cox-2 inhibitor seems to be able to reduce leukocytospermia and increase sperm count. (Fertil Steril® 2006;86:601–5. ©2006 by American Society for Reproductive Medicine.)

**Key Words:** Leukocytospermia, bacteriospermia, clinical signs of infection, antiinflammatory therapy, Cox-2 inhibitor

Bacteriospermia is commonly found in semen samples from infertile men, even in the absence of a clinically apparent male accessory gland infection (1–3). To reduce contamination, the World Health Organization (WHO) recommends hygienic preparation before delivering the semen sample (e.g., urination and washing the hands, penis, and scrotum) (4). Despite special procedures carried out before ejaculation, bacteria are only reduced in number and not eliminated. Enteric contaminants in particular may be reduced using antibacterial skin preparation (5).

Leukocytes are also commonly found in semen samples, and a level above  $1 \times 10^6/\text{mL}$  is considered pathologic according to WHO criteria (6). Whether a correlation exists between leukocytospermia and bacteriospermia remains controversial, particularly in asymptomatic men (7–10), and the presence of seminal bacteria may represent only contamination (11). Male accessory gland infection is said to be present by WHO if specific symptoms, e.g., urinary tract infection, epididymitis, sexually transmitted disease, thickened or

tender epididymis or vas deferens, or abnormal digital rectal examination, or ejaculate signs, e.g., leukocytospermia or bacteriospermia, are present (4). Infection is diagnosed if two signs of each group or both ejaculate signs are present.

Reports in the literature about treatment of leukocytospermia with an antiinflammatory medication are rare (12), although antioxidant treatment with carnitines or therapies with antihistamine-like drugs have recently been published (13, 14). Treatment of leukocytospermia might improve semen quality, as suggested by results from recently published work showing a negative effect of leukocytes and reactive oxygen species, which might be produced primarily by leukocytes, on semen quality (15–20).

One aim was to investigate a possible correlation between ejaculate and clinical signs of infection, bacterial growth in semen samples, and inflammatory signs in systemic blood. If bacteria are merely contaminants, no signs of clinical inflammation should be detectable. The second aim was to evaluate whether in the case that there is no correlation between bacteriospermia, leukocytospermia, and infection signs, an antiinflammatory prostaglandin inhibitory therapy with cyclooxygenase-2 (Cox-2) inhibitor can influence semen quality.

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## MATERIALS AND METHODS

A total of 56 men were studied after informed consent was obtained. The study was approved by the institutional review board. The patients were referred to the clinic because of failure to achieve pregnancy and required artificial insemination if semen quality was poor.

Blood samples were taken from the cubital vein of all patients for quantification of serum leukocyte count, serum C-reactive protein (CRP) and serum prostate-specific antigen (PSA). Normal blood serum levels were taken as 4.0–10.0 g/L for serum leukocyte count and <0.5 mg/dL for serum CRP, and the age-adjusted levels according to Oesterling et al. (21) were used for serum PSA. The men then underwent a detailed clinical examination including inspection and palpation of the penis, scrotum, and prostate, and a detailed medical history was taken.

All patients provided a semen sample for analysis and culture. Patients were instructed not to ejaculate for  $\geq 3$ –5 days before bringing in the sample. The men were asked to urinate before ejaculation and then to wash the hands, penis and scrotum with soap and water. Because there were a couple of days between the first consultation and the bringing in of the semen samples, an instruction letter was handed out as well. The patients were provided with a plastic cup with a wide opening and all samples were produced by masturbation.

Semen analysis was performed a maximum of 1 hour after ejaculation according to the WHO laboratory manual (6). Data were collected for sperm concentration, concentration of leukocytes, and patient age.

An apparent infection was diagnosed according to the WHO as described in the preceding paragraphs. In addition, all elevated systemic inflammation parameters (serum leukocyte count, serum CRP, and serum PSA above the age-correlated ranges) were regarded as signs of inflammation in systemic blood. Bacterial cultures were considered positive if the number of colony-forming units of pathogenic bacteria was  $1 \times \geq 10^3$ /mL.

All patients with sterile leukocytospermia were offered a 2-week therapy cycle with a specific Cox-2 inhibitor (valdecoxib, 20 mg) once daily. Twelve of the 34 patients participated in this therapy, and from these 12 patients semen analysis was repeated 12 weeks later. Changes of semen characteristics were the primary endpoint of the study 12 weeks after finishing medical treatment.

Statistical analysis was carried out using Statistical Package for the Social Sciences (version 10.0.7; SPSS, Chicago, IL) software. All demographic data were presented as the median and 25th and 75th quartiles. Statistical difference was assessed using the Mann-Whitney *U* test. A value of  $P < .05$  was taken to indicate statistical significance. Relationships between the different parameters were analyzed using the Spearman  $\rho$  correlation.

## RESULTS

Fifty-six patients were evaluated. Their median age was 35.5 years (range 31.3–38.8 years), and they had a median sperm concentration of  $6.5 \times 10^6$ /mL (range 3.1–16.4  $\times 10^6$ /mL). The median leukocyte concentration was  $1.2 \times 10^6$ /mL (range 0.6–3.2  $\times 10^6$ /mL). Leukocytospermia (leukocyte concentration  $> 1 \times 10^6$ /mL) was present in 60.7% of the samples, and 35.7% contained significant pathogenic bacterial growth. A total of 14.3% of the samples fulfilled the criteria for ejaculate signs of male accessory gland infection.

A summary of patient age and semen characteristics for men with bacteriospermia, leukocytospermia, and ejaculate signs of infection is shown in Table 1. No statistically significant difference in sperm concentration was found between samples with and without leukocytospermia ( $P = .075$ ), with and without bacterial growth ( $P = .112$ ), or with and without ejaculate signs of infection ( $P = .852$ ). The statistical difference for sperm morphology and motility between samples with and without leukocytospermia was  $P = .002$  and  $P = .056$ , respectively, in samples with and without bacteriospermia  $P = .032$  and  $P = .316$ , and in samples with and without ejaculate signs of infection  $P = .197$  and  $P = .988$ . The statistical differences for age and the presence of leukocytes (in the ejaculate) were similar in samples with and without leukocytospermia (age,  $P = .181$ ; leukocytes,  $P < 0.05$ ), with and without bacterial growth (age,  $P = .952$ ; leukocytes,  $P < 0.05$ ), and with and without ejaculate signs of infection (age,  $P = .269$ ; leukocytes,  $P = .424$ ).

The prevalence of pathogenic bacterial species was as follows: *Ureaplasma urealyticum*, 18.2%; enterococci, 13.6%; *Staphylococcus* spp., 15.9%; *Bacteroides* spp., 6.8%; *Escherichia coli*, 4.5%; *Streptococcus* spp., 4.5%; *Prevotella* spp., 4.5%; and *Enterobacter* spp., 2.3%.

None of the men had a recent history of any clinically apparent infection that could raise levels of serum leukocyte count, serum CRP, or serum PSA.

All blood serum parameters fell within normal ranges; the median serum leukocyte count level was 6.1 g/L (range 5.2–7.1 g/L), serum CRP was never elevated, and serum PSA levels (median 0.5 ng/mL, range 0.4–0.7 ng/mL) always fell within the age-adjusted reference ranges. There was no statistically significant difference in serum parameters between samples with and without leukocytospermia (serum leukocyte count,  $P = .903$ ; serum PSA,  $P = .583$ ), with and without bacteriospermia (serum leukocyte count,  $P = .077$ ; serum PSA,  $P = .362$ ), and with and without ejaculate signs of infection (serum leukocyte count,  $P = .640$ ; serum PSA,  $P = .483$ ).

Using the Spearman  $\rho$  correlation, no statistically significant correlation was found between the presence of bacteria and serum levels of leukocyte count ( $P = .077$ ) and serum PSA ( $P = .370$ ). Similar results were found for detection of leukocytospermia with serum leukocyte count ( $P = .905$ ) and

**TABLE 1****Semen characteristics of 56 semen samples.**

Condition	Age (y)	Sperm concentration ( $10^6$ /mL)	Normal morphology (%)	Motile sperm (%)	Leukocyte concentration ( $10^6$ /mL)
Bacteriospermia					
Positive (n = 20)	35.5 (29.3–41.5)	4.9 (2.8–8.5)	60.0 (51.0–66.0)	35.0 (18.5–60.8)	0.8 (0.5–1.0)
Negative (n = 36)	35.5 (32.3–38.0)	8.3 (3.2–21.0)	48.0 (22.0–64.0)	24.0 (11.5–54.0)	0.6 (0.8–4.4)
Leukocytospermia					
Positive (n = 34)	36.0 (32.8–38.5)	7.9 (3.8–21.0)	46.0 (22.0–60.5)	20.0 (9.8–51.8)	2.8 (1.3–4.6)
Negative (n = 22)	35.0 (29.8–39.0)	4.7 (1.7–10.2)	64.0 (52.0–66.8)	37.0 (20.0–71.8)	0.5 (0.3–0.8)
Ejaculate signs of infection					
Positive (n = 8)	38.5 (32.0–45.0)	5.9 (4.3–10.8)	60.0 (52.0–66.0)	27.5 (15.0–55.3)	1.4 (1.0–2.6)
Negative (n = 48)	35.5 (30.8–38.0)	6.7 (3.0–18.5)	51.5 (28.9–65.0)	30.5 (16.3–59.8)	1.1 (0.5–3.4)

Note: Data are median and 25th–75th quartiles.

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serum PSA ( $P=.547$ ) and for ejaculate signs of infection with serum leukocyte count ( $P=.645$ ) and serum PSA ( $P=.492$ ). Because serum CRP was negative in all blood samples no correlation could be calculated using that parameter.

Demographic results from the patients with abacterial leukocytospermia who received further antiinflammatory treatment (12 of 34) were as follows. The median age was 36.0 years (range 35.0–37.8 years), sperm concentration  $45.0 \times 10^6$ /mL (range  $21.0$ – $50.0 \times 10^6$ /mL) and semen leukocyte concentration  $2.5 \times 10^6$ /mL (range  $1.0$ – $5.8 \times 10^6$ /mL). The results of the consecutive semen analysis after treatment are shown in Table 2, where a statistically significant improvement in sperm concentration and reduction of leukocyte concentration was found.

## DISCUSSION

In this study the median sperm concentration in semen was  $6.5 \times 10^6$ /mL (range  $3.1$ – $16.4 \times 10^6$ /mL), so this group of men cannot be compared with the general population. Men attending the Andrology Department of the

University Clinic of Urology usually have poor semen quality and require artificial insemination (22). However, most studies on leukocytospermia and bacterial infection have been carried out on this kind of population, particularly in relation to investigations of the cause of poor semen quality (7–11). Our results are, therefore, similar to other data in the literature. Leukocytospermia (sperm concentration  $>1 \times 10^6$ /mL) was present in 60.7% of the semen samples, significant growth of pathogenic bacteria was found in 35.7%, and WHO criteria for ejaculate signs of infection were met in 14.3% of cases.

To reduce the number of false positive bacterial cultures WHO recommends hygienic preparation, such as urination and washing the hands, penis, and scrotum with soap and water before delivering semen. The WHO criteria differentiate between ejaculate signs and clinical or physical and medical history signs of infection, which together lead to diagnosis of a male accessory gland infection. None of the clinical or physical and medical history signs were positive in this study. The blood serum parameters investigated (se-

**TABLE 2****Semen characteristics from 12 patients before and after treatment with a Cox-2 inhibitor.**

Characteristic	Before treatment	After treatment	P
Sperm concentration ( $10^6$ /mL)	22.5 (7.5–39.8)	48.0 (45.8–80.0)	.02
Normal morphology (%)	20.0 (15.8–27.3)	36.0 (14.5–51.0)	.266
Motile sperm (%)	28.0 (12.0–32.8)	33.5 (13.8–42.0)	.178
Leukocyte concentration ( $10^6$ /mL)	5.5 (3.3–6.8)	1.0 (0.3–2.0)	.001

Note: Data are median and 25th–75th quartiles and Mann-Whitney U test.

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rum leukocyte count, serum CRP, and serum PSA) were within normal ranges, supporting the absence of acute infection. Even in semen samples where criteria for an ejaculate infection were met (14.3%), blood serum parameter levels and clinical evaluation results were not pathologic. Bacteriospermia may, therefore, represent merely contamination or the beginning of inflammation before clinical and laboratory symptoms appear.

The presence of contamination in semen samples is confirmed in a study by Cottell et al. (11) in which 60 men starting an IVF program were investigated. Pathogenic bacteria grew in 51% of semen samples, 37% of first-catch urine samples, and 27% of midstream urine samples. The mean semen leukocyte concentration was  $0.98 \times 10^6/\text{mL}$ , and only six men had leukocytospermia (sperm concentration  $>1 \times 10^6/\text{mL}$ ). Ten percent of these would have an infection according to the WHO ejaculate signs of infection. Their mean leukocyte level was rather low compared with that in our study (median of  $2.8 \times 10^6/\text{mL}$  [ $1.3\text{--}4.6 \times 10^6/\text{mL}$ ]).

Another study referring to bacterial contamination is that of Kim and Goldstein (5). Fourteen patients delivered semen samples with and without antibacterial skin preparation with 4% chlorhexidine and 10% povidone-iodine. A significant reduction in the number of enteric bacteria could be achieved with this method. Semen parameters and leukocyte concentration in the semen samples were not described, so results for ejaculate signs of infection could not be compared.

Male accessory gland infections, such as epididymitis and orchitis, lead at least temporarily to deterioration in spermatogenesis (23). Both the infection itself and the bacteria may reduce semen quality (24). Semen parameters other than leukocyte concentration, e.g., pH and viscosity, are then disturbed. In our study, no statistically significant difference between men with and without leukocytospermia and bacteriospermia was found in any semen parameters investigated whether or not ejaculate signs of infection were present. Although semen concentration in this study population was low, there was no statistically significant difference between any comparison group. No correlation between leukocytospermia, bacteriospermia, and ejaculate signs of infection with any semen parameter was found. Because of these results we concluded that leukocytospermia and bacteriospermia in infertile men may be two independent observations, especially if no clinical sign of infection is present.

However, in recent years many reports have been published showing that reactive oxygen species which were produced by leukocytes might cause bad semen quality, especially DNA damage and defects of sperm morphology (15–20). Antibiotic treatment showed only poor improvement or led to reinfection with antibiotic-resistant bacteria (25–29). Therefore antioxidants and antiinflammatory drugs might show better results. Vicari et al. (13) published a study on antioxidant treatment with carnitines for patients with prostatovesiculoe epididymitis, showing the highest reduction of reactive oxygen species and an improvement of sperm

motility and viability in the group of patients who received nonsteroidal antiinflammatory treatment for 2 months followed by 2 months treatment with carnitines. In contrast to our study, all patients were asymptomatic, ejaculate signs of infection were incidental findings, and only one drug was used. In addition, we found a significant increase in sperm count.

Another recently published article dealing with this topic, by Oliva and Mulitgner (14), described an improvement of sperm morphology and motility in infertile males with leukocytospermia using ketotifen, an antihistamine-like drug, which has a stabilizing effect on mast cells. Leukocytospermia decreased from a median  $5 \times 10^6/\text{mL}$  to a median of  $0 \times 10^6/\text{mL}$  after 4 weeks of treatment. But sperm concentration did not change during this study, and sperm count decreased after treatment ( $41 \times 10^6/\text{mL}$  to  $36 \times 10^6/\text{mL}$ ).

Consequently, because therapeutic options are still lacking for leukocytospermia, patients with abacterial leukocytospermia were offered a Cox-2 inhibitor once daily for 2 weeks in the present study. This therapy option was offered to this special group of patients because of a possible negative side effect of an antiinflammatory prostaglandin inhibitory medication to the immune response in patients with bacteriospermia, according to published reports (13–14). The results as shown in Table 2 were promising. We could show on the one hand an increase of sperm count and on the other hand a decline in leukocyte counts. Both investigations were statistical significant ( $P=.02$  and  $P=.001$ ). This finding of increasing sperm count after antiinflammatory therapy has not been reported before. In addition, we found improvement in sperm morphology and motility, though not statistically significant.

Our new data show that an antiinflammatory therapy alone, especially a selective Cox-2 inhibitor, in abacterial leukocytospermia can result in an improvement of semen quality.

## CONCLUSIONS

The results of this study show that bacteria grown from semen samples might only be contaminants from the genital tract. This is confirmed by the absence of an immune response in the peripheral blood system, the absence of clinical signs, and the lack of significant differences in semen parameters between men with and without leukocytospermia, bacteriospermia, and ejaculate signs of infection. A Cox-2 inhibitor may be a therapeutic option for patients with abacterial leukocytospermia, showing a reduction of semen leukocytes and an increase in sperm count.

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