The Effect of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) on Semen Parameters in Human Males: A Systematic Review and Meta-Analysis

Weihua Fu¹, Zhansong Zhou¹, Shijian Liu², Qianwei Li¹, Jiwei Yao¹, Weibing Li¹*, Junan Yan¹*

1 Department of Urology, Southwest Hospital, Third Military Medical University, Chongqing, People’s Republic of China, 2 Institute for Pediatric Translational Medicine, Shanghai Children’s Medical Center, Shanghai Jiaotong University School of Medicine, Shanghai, People’s Republic of China

Abstract

Background: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is one of the risk factors of impaired male fertility potential. Studies have investigated the effect of CP/CPPS on several semen parameters but have shown inconsistent results. Hence, we performed a systematic literature review and meta-analysis to assess the association between CP/CPPS and basic semen parameters in adult men.

Methods: Systematic literature searches were conducted with PubMed, EMBASE and the Cochrane Library up to August 2013 for case-control studies that involved the impact of CP/CPPS on semen parameters. Meta-analysis was performed with Review Manager and Stata software. Standard mean differences (SMD) of semen parameters were identified with 95% confidence intervals (95% CI) in a random effects model.

Results: Twelve studies were identified, including 999 cases of CP/CPPS and 455 controls. Our results illustrated that the sperm concentration and the percentage of progressively motile sperm and morphologically normal sperm from patients with CP/CPPS were significantly lower than controls (SMD (95% CI) −14.12 (−21.69, −6.63), −5.94 (−8.63, −3.25) and −8.26 (−11.83, −4.66), respectively). However, semen volume in the CP/CPPS group was higher than in the control group (SMD (95% CI) 0.50 (0.11, 0.89)). There was no significant effect of CP/CPPS on the total sperm count, sperm total motility, and sperm vitality.

Conclusions: The present study illustrates that there was a significant negative effect of CP/CPPS on sperm concentration, sperm progressive motility, and normal sperm morphology. Further studies with larger sample sizes are needed to better illuminate the negative impact of CP/CPPS on semen parameters.

Introduction

Prostatitis is a common male urogenital disease with prevalence ranging from 2.2% to 9.7% worldwide, with an overall rate of 8.2% [1]. A heterogeneous mixture of syndromes defines prostatitis, with broad diagnostic criteria and a vague understanding of its etiology and pathophysiology [2,3]. To improve its clinical diagnosis, the National Institutes of Health (NIH) classifies prostatitis into four categories, namely, I: acute bacterial prostatitis, II: chronic bacterial prostatitis, III: chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and IV: asymptomatic inflammatory prostatitis [4].

CP/CPPS accounts for more than 90% of all symptomatic prostatitis cases in urology outpatient clinics [4]. It is characterized by chronic pelvic pain symptoms, which lasted at least 3 months during the previous 6 months, in the absence of a urinary tract bacterial infection but in the presence of urinary symptoms and sexual dysfunction [4,5]. These symptoms seriously affect the quality of life of patients [6,7]. Based on the presence or absence of leukocytes in prostatic secretions (EPS), postprostatic massage urine (VB3), or semen, CP/CPPS is further subdivided into two subtypes: NIH IIIA (inflammatory) and NIH IIIB (noninflammatory) [4,8]. Traditionally, symptomatic prostatitis without bacteriuria was defined as nonbacterial prostatitis (inflammatory) or prostatodynia (noninflammatory) on the basis of leukocytes in EPS [9]. Compared with the traditional EPS-based classification, NIH IIIA encompasses a larger range of patients than nonbacterial prostatitis due to its broader criteria for inflammation. In other words, patients diagnosed with prostatodynia may be categorized into the NIH IIIB or NIH IIIA subgroup [10,11].

During the past decade, the incidence of male accessory gland infection (MAGI) as a potential etiologic factor in male subfertility or infertility has increased [12,13]. Adverse factors, including pathogenic bacteria, leukocytes, cytokines, reactive oxygen species (ROS), obstruction and immunological allergic effects, might be involved in the development of infertility resulting from MAGI [13,14]. As one of the main clinical categories of MAGI, chronic
prostatitis can also affect male fertility [14–16]. For example, 
*Chlamydia trachomatis* infection is related to poor semen quality in 
prostatitis patients [17–19]. However, as for the negative effect of 
CP/CPPS on semen quality, published studies present conflicting 
results, with some studies showing statistically significant alter-
ations of basic semen parameters due to CP/CPPS [20–23], but 
not others [24,25]. Therefore, we systematically reviewed the 
available literature and performed a meta-analysis to evaluate the 
association between CP/CPPS and basic semen parameters in 
adult men, which might shed valuable insights on the treatment of 
infertility.

**Methods**

**Literature search**

This meta-analysis was restricted to published studies that 
investigated the effect of CP/CPPS on semen parameters during 
male reproductive age. Two independent reviewers (Li QW and 
Yao JW) searched PubMed, EMBASE, and the Cochrane Library 
from inception to August 2013, without restrictions on language or 
study type. The search terms combined text words and MeSH 
terms. For example, the search terms for CP/CPPS were 
prostatitis, prostatism, chronic prostatitis, chronic pelvic pain 
syndrome, abacterial prostatitis, nonbacterial prostatitis, and 
prostatodynia, while those for semen parameters were semen, 
sperm, spermatozoon, spermatozoon, semen analysis, sperm count, 
spermatozoon count, sperm motility, spermatozoon motility, and 
spermatozoon density. All related articles and abstracts were 
retrieved. In addition, references cited within relevant reviews 
were retrieved by hand.

**Eligibility criteria**

**Inclusion criteria.** Studies were included if patients met 
diagnostic criteria for CP/CPPS according to the NIH classification 
or the traditional definition of nonbacterial prostatitis and 
prostatodynia. The controls were healthy human males. Semen 
samples were obtained before therapeutic intervention and 
analyzed according to World Health Organization (WHO) 
criteria. Semen parameters included seminal plasma volume, 
sperm concentration (density), total sperm count, motility, vitality 
and morphology. Available data were extracted from the article, 
including means and standard deviations of sperm parameters in 
all case-control groups.

**Exclusion criteria.** Studies were excluded if they were case 
reports. Studies involving patients with chronic prostatitis accom-
panied by other disorders of the urogenital system, patients that 
had previously undergone surgery of the genital system, and 
patients previously diagnosed with azoospermia or infertility were 
excluded. Studies involving patients with a mean age of <12 years 
old or >60 years old were also excluded [26].

**Study selection and validity assessment**

Two independent reviewers (Li QW and Yao JW) screened titles 
and abstracts of all citations from the literature search. All relevant 
studies that appeared to meet eligibility criteria were retrieved. Full 
texts were needed to analyze if an ambiguous decision was made 
based on the title and abstract. The final decision of eligible studies 
was made by reviewing articles. Disagreements were resolved by 
consensus or a third reviewer (Zhou ZS). Two reviewers (Liu SJ 
and Zhou ZS) completed the quality assessment according to the 
primary criteria for nonrandomized and observational studies of
Table 1. Characteristics of included studies investigating the effect of CP/CPPS on semen parameters.

| Study                  | Country      | Mean age (case/control) | Abstinence time (days) | IIIA (n) | IIIB (n) | III (n) | Control (n) | Semen parameters | Criterion for semen analysis |
|------------------------|--------------|-------------------------|-----------------------|--------|--------|--------|------------|------------------|-----------------------------|
| Ausmees et al. 2008    | Estonia      | 55.3/56.1               | 5.9                   | 3.8    | 213    | 35     | 1999/2010   | WHO manual        | SV, TSC, SC, SPM, SNM      |
| Zhao et al. 2008       | China        | 30.3/28.9               | 3–7                   | 60     | 20     | 15     | 1999 a      | WHO manual        | SV, SC, SPM, SpV          |
| Motrich et al. 2006    | Argentina    | 40.41/32.18             | 2–7                   | 25     | 24     | 24     | 1999 WHO    | Manual            | SC, SPM, SpV, STM, SNM    |
| Wang et al. 2006       | China        | 35/32                   | 5–7                   | 74     | 46     | 46     | 1999 WHO    | Manual            | SC, SPM, SpV, STM, SNM    |
| Henkel et al. 2006     | Germany      | NI                      | NI                    | 24     | 32     | 24     | 1999/1992   | WHO manual        | SC, SPM, SpV, STM, SNM    |
| Motrich et al. 2005    | Argentina    | 41.41/32.18             | 2–7                   | 29     | 15     | 15     | 1999/1992   | WHO manual        | SC, SPM, SpV, STM, SNM    |
| Zhang et al. 2004      | China        | 27.5–55.3               | 3–7                   | 86     | 18     | 18     | 1999 a      | WHO manual        | SV, SC, SPM, SpV, STM, SNM|
| Menkveld et al. 2003   | Germany      | 27.5/NI                 | Ni                    | 34     | 30     | 30     | 1999/1992   | WHO manual        | SV, SC, SPM, SpV, STM, SNM|
| Engberg et al. 2000    | Switzerland  | 27.5/NI                 | Ni                    | 34     | 30     | 30     | 1999/1992   | WHO manual        | SV, SC, SPM, SpV, STM, SNM|
| Pasquale et al. 2006   | USA          | 5                      | > 2                   | 2      | 17     | 17     | 1999 a      | WHO manual        | SV, SC, SPM, SpV, STM, SNM|
| Leib et al. 1994       | Israel       | 27.5/NI                 | Ni                    | 2      | 12     | 12     | 1999/1992   | WHO manual        | SV, SC, SPM, SpV, STM, SNM|
| Widmer et al. 1991     | Germany      | 40.2/39.5               | > 7                   | 4      | 42     | 42     | 1999 WHO    | Manual            | SV, SC, SPM, SpV, STM, SNM|

Abbreviations: SpV, semen volume; SC, sperm concentration (density); TSC, total sperm count; SPM, progressive sperm motility; STM, total sperm motility; SpV, sperm vitality; SNM, normal sperm morphology; IIIA, NIH IIIA subgroup; IIIB, NIH IIIB subgroup; III, NIH III subgroup; NI, not indicated in studies; a: confirmed by the authors.

The Newcastle-Ottawa Quality Assessment scale (NOS) in meta-analyses [27].

Data extraction and statistical analysis

Data, including demographic data (authors, year of publication, country, number and mean age of participants, and abstinence time) and outcome data of semen parameters (semen volume, sperm concentration, total sperm count, sperm progressive motility, sperm total motility, sperm vitality, and sperm normal morphology), were extracted from the studies by three reviewers (Li QW, Yao JW and Zhou ZS). Disagreements were resolved by consensus.

Quantitative meta-analysis was performed by two reviewers (Li SJ and Fu WH) with Review Manager (RevMan) software (version 5.2.5, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen) and Stata software (version 12.0, College Station, Texas, USA). Semen parameter data were analyzed in the meta-analysis. To better understand the effect of CP/CPPS on semen parameters, patients were classified into three subgroups according to the NIH classification: NIH IIIA, NIH IIIB or NIH III (the subgroup of unclassified CP/CPPS) in our study. We pooled the standard mean differences (SMD) of semen parameters of the case-control groups, which were identified with 95% confidence intervals (95% CI). Heterogeneity was assessed by the P-value and the I-square statistic ($I^2$) in the pooled analyses, which represents the percentage of total variation across studies [28]. If the P-value was less than 0.05 or the $I^2$-value was greater than 50%, the summary estimate was analyzed in a random-effects model. Otherwise, a fixed-effects model was applied. In addition, publication bias was detected by visual symmetry of funnel plots, with asymmetry suggesting possible publication bias. It was also assessed by the Begg's and Egger's test in the meta-analysis. If the P-value was less than 0.05, publication bias existed.

Results

Characteristics of the included studies

Figure 1 shows a detailed review process. A total of 933 nonduplicate studies were identified. Twelve studies were ultimately selected according to eligibility criteria (Table 1). Of these, five [25,29–32], four [29,31,33,34], and eight [25,29,32,35–39] studies investigated the effects of NIH IIIA, NIH IIIB, and NIH III (unclassified CP/CPPS) on semen parameters, respectively. All retrieved studies involved 999 CP/CPPS cases and 455 controls.

Table 1 summarizes general data from the twelve studies. The mean ages of patient and control groups were in the ranges of 27.5–55.3 years and 28.9–56.1 years, respectively. The mean ages of patient and control groups were unavailable for three studies [30–32]. All but one of these studies reported exclusion/inclusion criteria [31]. Nine out of twelve studies included the abstinence time before semen collection [25,30,32,33,35–39]. Semen analysis was performed according to WHO criteria. Two studies [31,37] also evaluated sperm morphology according to stringent criteria described by Menkveld and Kruger [40,41], in order to comparing with the results assessed by the 1992 WHO manual. These data were not included in this meta-analysis.

Meta-analysis

Data of seven semen parameters were respectively analyzed in a random-effects model to estimate the effect of CP/CPPS on each parameter. The results suggested that sperm concentration and the percentage of progressively motile sperm and morphologically normal sperm from patients with CP/CPPS were significantly
lower than controls. Pooled SMD (95% CI) were -14.12 (-21.69, -6.63), -5.94 (-8.63, -3.25), and -8.26 (-11.83, -4.66), respectively. There was evidence of significant heterogeneity among these studies (P < 0.00001, I2 = 92%). Test for overall effect: Z = 1.51 (P = 0.13)

1.6.2 Subgroup analysis was performed simultaneously. There was a statistically significant difference in the same four semen parameters between the NIH III subgroups and the control groups. Pooled SMD and 95% CI for semen volume, sperm concentration, sperm progressive motility, and normal sperm morphology were 0.62 (0.03, 1.21), -18.98 (-26.14, -11.82), -5.69 (-8.44, -2.94), and -9.68 (-14.65, -4.71), respectively. There was evidence of significant heterogeneity among these studies (P < 0.00001, I2 = 79%). There was evidence of significant heterogeneity among these studies (P = 0.01, I2 = 50%) (Figures 2, 3, 4). However, there was no significant difference in any of the semen parameters according to subgroup analysis of the NIH IIIA and the NIH IIIB, except for the percentage of sperm total motility in the NIH IIIA subgroup (SMD (95% CI): 6.39 (1.56, 11.21)). There was no evidence of significant heterogeneity among these studies (P = 0.64, I2 = 0%) (Figure 6).

Discussion

In this study, twelve available published articles were reviewed and analyzed statistically to investigate the effect of CP/CPPS on seven semen parameters. The results of this meta-analysis suggested that CP/CPPS significantly reduced sperm concentration, sperm progressive motility, the percentage of normal sperm morphology, and increased semen volume of patients compared with controls. The relationship between CP/CPPS and total sperm count, sperm total motility, and sperm vitality was not identified.

Basic semen parameters are still the mainstay of male fertility and reproductive health assessment [42,43]. For example, the percentage of morphologically normal sperm is an important indicator of male fertility potential and testicular stress [44]. Poor sperm morphology characterized by poor chromatin condensation, acrosome reaction, or DNA integrity is related to sperm dysfunction [45]. In our review, nine studies investigated the effect of CP/CPPS on normal sperm morphology. Positive results were shown in five studies [29,30,37–39], but not in the remaining four studies [31,32,34,35]. Our results illustrate that CP/CPPS associated with a significant decline in the percentage of morphologically normal sperm (Figure 2), which is consistent with a previous literature review [12].

It is noteworthy that there is a downward trend in the percentage of morphologically normal sperm with the published time of the included studies, especially the very low percentage (6.0% for controls) reported by Ausmees et al. [35]. Besides
negative environmental and socio-psycho-behavioral factors [46,47], the heterogeneity of normal sperm morphology is mainly due to the implementation of strict criteria and additional criteria for sperm morphology evaluation [47]. Evaluation criteria of sperm morphology has passed through two phases, liberal and strict criteria [48]. In the five consecutive editions of the WHO laboratory manual, liberal criteria were adopted in the 1980 and 1987 manuals [49,50], and strict (Tygerberg) criteria were accepted in part in the 1992 manual [51] and recommended in the 1999 and 2010 manuals [43,52]. Owing to the increasingly stringent criteria, the cut-off reference values for normal sperm morphology were significantly reduced from 80.5% in the 1980 WHO manual to 4% in the 2010 WHO manual [43,49].

Some studies have argued that very low normal sperm morphology evaluated with strict criteria limits its clinical value in investigating male fertility potential [53–55]. To make up for this deficiency, additional sperm morphology parameters such as abnormal sperm morphology, acrosome index (AI), teratozoospermia index (TZI), and sperm pattern defects have been studied [47].

Sperm concentration is an important indicator of semen quality. An enhanced level of DNA damage was observed in semen samples with low sperm concentrations [56]. However, there is no linear relationship between sperm concentration and fecundity. Previous studies reported a decrease in male fertility when the sperm concentration was below the threshold value, the range of which is $15 \times 10^6$/ml to $55 \times 10^6$/ml [57–60]. In the most recent WHO manual, a normal sperm concentration is $15 \times 10^6$/ml [43]. However, sperm concentration is dependent on semen volume to some extent. Therefore, total sperm count might be a better indicator of normal spermatogenesis. It was not only positively correlated with testis size [61], but also with the time interval from wish of pregnancy to pregnancy obtained [62].

In this review, the sperm concentration was measured in eleven out of twelve studies [25,29–38]. Statistically significant differences were found between case and control groups in only two studies [31,38], in which the patients were respectively diagnosed with NIH IIIB and chronic nonbacterial prostatitis with positive lymphoproliferative autoimmune response against prostate antigens. The pooled SMD result suggested a statistically significant decrease in sperm concentration in the CP/CPPS group (Figure 3). However, owing to the significant increase in semen volume in patients with CP/CPPS, a statistically significant difference in total sperm count was not found in the CP/CPPS group compared to the control group in our meta-analysis (Figure 8). It should point out that the data of total sperm count was shown in only two included studies [35,39]. Other two included articles also involved it, but without the exact values in texts [29,32]. Contradictory
conclusions were drawn in these four studies, and only Henkel et al. reasoned that total sperm counts were significantly reduced in NIH IIIA and NIH IIIB groups compared to control groups (P<0.01) [29].

Sperm motility is essential for fertilization. Impaired sperm motility is significantly associated with unstable DNA/RNA and mitochondrial dysfunction [63–66], which reduce the successful fertilization rate. Therefore, the percentage of motile sperm is a good indicator of male fertility potential [67,68]. To identify the subfertile males, the 2010 WHO manual defines the reference limit for total motility at 40% and progressive motility at 32%, and males with sperm motility values below these threshold values are asthenozoospermic [43]. Similar threshold values were reported in a previous review [59].

Infection and inflammation of the male genitourinary tract is detrimental to sperm motility. Biological and biochemical changes in seminal plasma such as the presence of leukocytes, ROS and inflammatory cytokines can impair sperm motility and fertility potential [69]. A recent review also concluded that there might be a negative impact of CP/CPPS on sperm motility [12]. In this review, all included studies revealed that sperm motility was decreased by different degrees in men with CP/CPPS, except for one study with contradictory results [31]. According to the meta-analysis, the percentage of progressive motile sperm was significantly lower in the CP/CPPS group than in the control group (Figure 4), but an adverse effect on motile total sperm was not found.

figure 4. Forest plot showing the meta-analysis outcomes of the effect of CP/CPPS on sperm progressive motility. doi:10.1371/journal.pone.0094991.g004

Sperm vitality is defined as the percentage of live spermatozoa [43]. It can be used to differentiate between necrozoospermia and total asthenozoospermia, and evaluate cellular membrane integrity and abnormal flagella [70]. In our review, seven studies reported conflicting sperm vitality results [29,31,33,36–39]. Only Zhao et al. reported a significant decrease of sperm vitality in CP/CPPS patients compared with controls (P<0.05) [36]. However, in this meta-analysis, the association between CP/CPPS and semen vitality was not identified (Figure 7).

Subgroup analysis was also performed in our study. In the meta-analysis of two subgroups (NIH IIIA and NIH IIIB), the results illustrated little effect of the two CP/CPPS subtypes on seven semen parameters, except for a significant increase in sperm total motility in the NIH IIIA subgroup, which are inconsistent with the total outcomes of the meta-analysis. The reasons for the conflicting results may be that there are not sufficient valid data for the meta-analysis of the two subgroups, since only five studies involving 251 NIH IIIA patients and four studies involving 154 NIH IIIB patients were included. Moreover, not all semen parameters were investigated in individual studies. In addition, data of semen parameters were inconsistent among the only few studies.

Although the relationship between CP/CPPS and male infertility has always been controversial, a voluminous literature suggests that CP/CPPS may negatively affect sperm parameters in many ways, including seminal oxidative stress, inflammatory cytokines and autoimmune responses. Excessive ROS and lower total anti-oxidant capacity (TAC) was found in all patients with
CP/CPPS compared with normal controls [32]. The increased seminal oxidative stress correlates with impaired sperm motility which was mentioned above, furthermore, it induces chromatin cross-linking, DNA strand breaks and peroxide-mediated sperm plasma membrane damage, which accelerates apoptosis and affects normal sperm morphology [71,72]. In addition, the

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV. Random. 95% CI | Mean Difference | IV. Random. 95% CI |
|-------------------|------|----|-------|------|----|-------|--------|-------------------|-----------------|------------------|
| 1.1.1 IIA         |      |    |       |      |    |       |        |                  |                 |                  |
| Mankveld 2003     | 3.08 | 1.7 | 34    | 3.45 | 2.1 | 17    | 6.3%   | -0.37 [-1.52, 0.78] |                |                  |
| Zhang 2004        | 3.02 | 1.0425 | 86    | 2.813 | 1.061 | 40    | 12.5%   | 0.21 [0.19, 0.60] |                |                  |
| Subtotal (95% CI) | 120  | 57 | 18.8% | 0.15 [-0.23, 0.52] |                |                  |
| Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 1 (P = 0.35); ι² = 0% |
| Test for overall effect: Z = 0.76 (P = 0.44) |

| 1.1.2 IIIB        |      |    |       |      |    |       |        |                  |                 |                  |
| Engeler 2003      | 4.3  | 1.8 | 30    | 3.2  | 1.3 | 30    | 8.9%   | 1.10 [0.31, 1.89] |                |                  |
| Mankveld 2003     | 2.98 | 1.7 | 18    | 3.45 | 2.1 | 17    | 5.6%   | -0.47 [-1.74, 0.80] |                |                  |
| Wang 2006         | 3.7  | 1.3 | 74    | 3    | 1.1 | 46    | 12.2%   | 0.70 [0.27, 1.13] |                |                  |
| Subtotal (95% CI) | 122  | 93 | 26.7% | 0.61 [-0.03, 1.26] |                |                  |
| Heterogeneity: Tau² = 0.17; Chi² = 4.23, df = 2 (P = 0.12); ι² = 53% |
| Test for overall effect: Z = 1.86 (P = 0.06) |

| 1.1.3 III         |      |    |       |      |    |       |        |                  |                 |                  |
| Ausness 2013      | 3.6  | 2   | 213   | 3.4 | 1.7 | 35    | 10.5%   | 0.20 [-0.42, 0.82] |                |                  |
| Leib 1994         | 3.4  | 1.9 | 86    | 2.6  | 1.5 | 101   | 11.6%   | 0.80 [0.30, 1.30] |                |                  |
| Motrich 2005      | 3.49931034 | 2.57828754 | 29 | 2.57 | 1.01 | 30 | 7.3%   | 0.93 [-0.08, 1.93] |                |                  |
| Motrich 2006      | 3.83 | 0.58 | 25 | 2.57 | 0.28 | 15 | 13.4% | 1.26 [0.99, 1.53] |                |                  |
| Zhao 2008         | 3.133 | 1.065 | 60 | 3.225 | 0.939 | 20 | 11.7% | -0.09 [-0.58, 0.40] |                |                  |
| Subtotal (95% CI) | 413  | 201 | 54.4% | 0.62 [0.03, 1.21] |                |                  |
| Heterogeneity: Tau² = 0.37; Chi² = 27.32, df = 4 (P = 0.0001); ι² = 85% |
| Test for overall effect: Z = 2.06 (P = 0.04) |

| Total (95% CI)    | 655  | 351 | 100.0% | 0.50 [0.11, 0.89] |                |                  |
| Heterogeneity: Tau² = 0.27; Chi² = 43.08, df = 9 (P < 0.0001); ι² = 79% |
| Test for overall effect: Z = 2.53 (P = 0.01) |
| Test for subgroup differences: Chi² = 2.59, df = 2 (P = 0.27), ι² = 22.8% |

Figure 5. Forest plot showing the meta-analysis outcomes of the effect of CP/CPPS on semen volume.
doi:10.1371/journal.pone.0094991.g005

CP/CPPS compared with normal controls [32]. The increased seminal oxidative stress correlates with impaired sperm motility which was mentioned above, furthermore, it induces chromatin cross-linking, DNA strand breaks and peroxide-mediated sperm plasma membrane damage, which accelerates apoptosis and affects normal sperm morphology [71,72]. In addition, the

| Study or Subgroup | Case Mean | SD | Total | Control Mean | SD | Total | Weight | IV. Random. 95% CI | Mean Difference | IV. Random. 95% CI |
|-------------------|-----------|----|-------|--------------|----|-------|--------|-------------------|-----------------|------------------|
| 1.2.1 IIA         |           |    |       |              |    |       |        |                  |                 |                  |
| Henkel 2006       | 63.3      | 12.9 | 24    | 57.4         | 4.6 | 95    | 17.0%  | 5.90 [0.66, 11.14] |                |                  |
| Mankveld 2003     | 70.5      | 18.2 | 34    | 61.4         | 22.6 | 17    | 10.9%  | 9.10 [-3.26, 21.46] |                |                  |
| Subtotal (95% CI) | 58        | 112 | 27.9% | 6.39 [1.56, 11.21] |                |                  |
| Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); ι² = 0% |
| Test for overall effect: Z = 2.59 (P = 0.009) |

| 1.2.2 IIIB        |           |    |       |              |    |       |        |                  |                 |                  |
| Engeler 2003      | 41        | 18  | 30    | 60           | 17 | 30    | 13.9%  | -19.00 [-27.86, -10.14] |                |                  |
| Henkel 2006       | 60.3      | 15.7 | 32    | 57.4         | 4.6 | 95    | 16.8%  | 2.90 [-2.62, 8.42] |                |                  |
| Mankveld 2006     | 70.6      | 23  | 18    | 61.4         | 22.6 | 17    | 9.0%   | 9.20 [-5.91, 24.31] |                |                  |
| Subtotal (95% CI) | 80        | 142 | 39.7% | -2.82 [-19.18, 13.53] |                |                  |
| Heterogeneity: Tau² = 181.81; Chi² = 19.28, df = 2 (P < 0.0001); ι² = 90% |
| Test for overall effect: Z = 0.34 (P = 0.74) |

| 1.2.3 III         |           |    |       |              |    |       |        |                  |                 |                  |
| Henkel 2006       | 61.6      | 14.5 | 56    | 57.4         | 4.6 | 95    | 18.0%  | 4.20 [0.29, 8.11] |                |                  |
| Motrich 2005      | 54.65310345 | 18.90857125 | 29 | 61.92 | 12.83 | 30 | 14.4% | -7.27 [-15.54, 1.01] |                |                  |
| Subtotal (95% CI) | 85        | 125 | 32.4% | -0.93 [-12.10, 10.24] |                |                  |
| Heterogeneity: Tau² = 54.85; Chi² = 6.03, df = 1 (P = 0.01); ι² = 83% |
| Test for overall effect: Z = 0.16 (P = 0.87) |

| Total (95% CI)    | 223        | 379 | 100.0% | 0.39 [-5.80, 6.57] |                |                  |
| Heterogeneity: Tau² = 51.34; Chi² = 31.98, df = 6 (P < 0.0001); ι² = 81% |
| Test for overall effect: Z = 0.12 (P = 0.90) |
| Test for subgroup differences: Chi² = 2.26, df = 2 (P = 0.32), ι² = 11.4% |

Figure 6. Forest plot showing the meta-analysis outcomes of the effect of CP/CPPS on sperm total motility.
doi:10.1371/journal.pone.0094991.g006
oxidative stress decreases acrosin activity and sperm-oocyte fusion capability [72].

Cytokines play a key role in the inflammatory response. Some inflammatory cytokines in seminal plasma of patients with CP/CPPS are increased significantly, such as IL-1, IL-6, IL-8, IL-10 and TNF-alpha, when compared with the normal group [73,74]. Lampiao et al. reported that seminal IL-6 significantly reduced sperm progressive motility, which was possibly due to overproduction of nitric oxide (NO) [75]. Similarly, Kopa Z and colleagues thought that seminal plasma IL-6 correlated negatively with sperm vitality and sperm motility [76]. Several studies investigated the effect of TNF-alpha on sperm parameters suggest that seminal plasma TNF-alpha adversely affects sperm motility and normal morphology via impairing sperm mitochondrial function, increasing NO production, inducing apoptosis [13,75]. As for the role of seminal IL-8, some research suggested it negatively correlated with total sperm count and sperm progressive motility [77,78]. Review the previous studies, the relationships between IL-1/10 and semen parameters remain unclear and need further investigation [13].

Another explanation for the alterations observed in semen parameters of patients with CP/CPPS is that autoimmune responses against prostate antigens may affect semen quality, including prostatic acid phosphatase (PAP), prostate steroid-binding protein (PSBP), prostate specific antigen (PSA) and other antigens in prostate homogenates and seminal plasma [79–81]. The autoimmune responses are considered to reduce sperm motility, counts, normal morphology and viability, and NO, ROS, TNF-alpha, IFN-gamma and other inflammatory mediators may be involved in the impact on semen parameters [38,81,82].

**Limitations**

There are some limitations in our study, which need to be taken into consideration when interpreting the results of this meta-analysis. First, there were differences among participants and methods, including differences in age and geographic locations of participants, different durations of abstinence before semen

| Study or Subgroup | Case Mean | SD | Total Mean | SD | Total Mean | SD | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|-----------|----|------------|----|------------|----|--------|-------------------------------|-------------------------------|
| Henkel 2006       | 82.8      | 9.7 | 24         | 78.5 | 27.6       | 95 | 6.2%   | 4.30 [-2.47, 11.07]            |                                |
| Menkveld 2003     | 81.1      | 11  | 34         | 77.2 | 12.3       | 17 | 6.0%   | 3.90 [-3.02, 10.82]            |                                |
| Subtotal (95% CI) | 83.1      | 14  | 78          | 75.7 | 12.7       | 17 | 6.0%   | 4.10 [-6.67, 9.14]             |                                |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.20, df = 1 (P = 0.94); I^2 = 0% | Test for overall effect: Z = 1.66 (P = 0.10) |

| Study or Subgroup | Case Mean | SD | Total Mean | SD | Total Mean | SD | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|-----------|----|------------|----|------------|----|--------|-------------------------------|-------------------------------|
| Henkel 2006       | 82.6      | 10.5 | 32         | 78.5 | 27.6       | 95 | 6.3%   | 4.10 [-2.54, 10.74]            |                                |
| Menkveld 2003     | 84.4      | 8.3  | 18         | 77.2 | 12.3       | 17 | 5.9%   | 7.20 [0.21, 14.19]             |                                |
| Wang 2006         | 57.3      | 11.1 | 74         | 60.1 | 11.3       | 46 | 11.7%  | -2.80 [-6.93, 1.33]            |                                |
| Subtotal (95% CI) | 73.4      | 14  | 141        | 64.2 | 10.5       | 50 | 10.9%  | -2.80 [-6.93, 1.33]            |                                |
| Heterogeneity: Tau^2 = 22.50; Chi^2 = 7.09, df = 2 (P = 0.03); I^2 = 72% | Test for overall effect: Z = 0.72 (P = 0.47) |

| Study or Subgroup | Case Mean | SD | Total Mean | SD | Total Mean | SD | Weight | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|-----------|----|------------|----|------------|----|--------|-------------------------------|-------------------------------|
| Henkel 2006       | 82.7      | 10.1 | 56         | 78.5 | 27.6       | 95 | 7.1%   | 4.20 [-1.95, 10.35]            |                                |
| Leib 1994         | 68.4      | 20.9 | 86         | 69.2 | 15.4       | 101| 8.6%   | -0.80 [-6.14, 4.54]            |                                |
| Molich 2005       | 83.15551724 | 7.51199042 | 29 | 83.7 | 7.7       | 30 | 12.5%  | -0.53 [-4.42, 4.35]            |                                |
| Molich 2006       | 83.1      | 1.6  | 25         | 83.7 | 2.1        | 15 | 22.7%  | -0.60 [-1.83, 0.63]            |                                |
| Zhao 2008         | 7.96      | 8.088 | 60         | 75.061 | 6.983      | 20 | 13.2%  | -4.20 [-7.87, -0.53]          |                                |
| Subtotal (95% CI) | 61.75     | 6.0  | 146        | 63.4 | 5.95       | 36 | 17.5%  | -4.20 [-7.87, -0.53]          |                                |
| Heterogeneity: Tau^2 = 1.48; Chi^2 = 5.95, df = 4 (P = 0.20); I^2 = 33% | Test for overall effect: Z = 0.93 (P = 0.35) |

**Figure 7. Forest plot showing the meta-analysis outcomes of the effect of CP/CPPS on sperm vitality.**
doi:10.1371/journal.pone.0094991.g007

**Figure 8. Forest plot showing the meta-analysis outcomes of the effect of CP/CPPS on total sperm counts.**
doi:10.1371/journal.pone.0094991.g008
collection, and different editions of the WHO manual for semen analysis, all of which may have affected the results of semen analysis [46,83–85]. Second, the sample size of each study was analyzed, all of which may have affected the results of semen collection, and different editions of the WHO manual for semen analysis [46,83–85].

In addition, semen volume was higher in the CP/CPPS group. Multicenter clinical trials with larger sample sizes are needed to validate these findings. Further studies that focus on differences in the two subtypes of CP/CPPS may also improve our understanding of CP/CPPS on semen parameters.

**Supporting Information**

**Checklist S1 PRISMA checklist.**

**Author Contributions**

Conceived and designed the experiments: WHF JAY WBL. Performed the experiments: WHF ZSZ SJL QHW JYW. Analyzed the data: WHF ZSZ SJL. Contributed reagents/materials/analysis tools: SJL ZSZ. Wrote the paper: WHF JAY WBL.

---

**References**

1. Krieger JN, Lee SW, Jeon PY, Long ML, et al. (2008) Epidemiology of prostatitis. Int J Antimicrob Agents 31 (Suppl 1): S85–90.
2. Sharp VJ, Takacs EB, Powell CR (2010) Prostatitis: diagnosis and treatment. Am Fam Physician 82(4): 397–406.
3. Pontari MA, Ruggieri MR (2008) Mechanisms in prostatitis/chronic pelvic pain syndrome. J Urol (Suppl 5): S61–67.
4. Krieger JN, Niberg L, Jr, Nickel JC (1999) NIH consensus definition and classification of prostatitis. JAMA 282(3): 216–237.
5. Pontari MA (2008) Chronic prostatitis/chronic pelvic pain syndrome. Urol Clin North Am 35(1): 81–89.
6. Ko JH, Kim SW, Paick JS (2005) Quality of life and psychological factors in chronic prostatitis/chronic pelvic pain syndrome. Urology 66(4): 693–701.
7. Berger KE (2005) Predictors of quality of life and pain in chronic prostatitis/chronic pelvic pain syndrome: findings from the National Institutes of Health Chronic Prostatitis Cohort Study. J Urol 174(5): 1842–1843.
8. Nickel JC (2003) Classification and diagnosis of prostatitis: a gold standard? Andrologia 35(3): 160–167.
9. Drach GW, Fair WR, Mares EM, Stamey TA (1978) Classification of benign disease associated with prostatic pain: prostatitis or prostatodynia? J Urol 120(2): 266.
10. Krieger JN, Jacobs RR, Ross SO (2000) Does the chronic prostatitis/pelvic pain syndrome differ from nonbacterial prostatitis and prostatodynia? J Urol 164(5): 1539–1548.
11. Krieger JN, Ross SO, Deutsch L, Riley DE (2002) The NIH Consensus concept of chronic prostatitis/chronic pelvic pain syndrome compared with traditional concepts of nonbacterial prostatitis and prostatodynia. Curr Urol Rep 3(4): 301–305.
12. Ross A, Platz A, Wagnerlehner F, Liu N, Diemer T, et al. (2012) Influence of urogenital infections and inflammation on semen quality and male fertility. World J Urol 30(1): 23–30.
13. La Vignera S, Vicari E, Condorelli RA, D’Agata R, Calogero AE (2011) Male accessory gland infection and sperm parameters. Int J Androl 34(3 Pt II): 330–347.
14. Everaert K, Mahmoud A, Depuydt C, Maeyaert M, Coenhove F (2003) Chronic prostatitis and male accessory gland infection—Is there an impact on male infertility (diagnosis and therapy)? Andrologia 35(3): 325–330.
15. Fraczk M, Kurpiz M (2007) Inflammatory mediators exert toxic effects of oxidative stress on human spermatozoa. J Androl 28(2): 325–333.
16. Shineld AW, Naughton CK (2004) Prostatitis and male factor infertility: a review of the literature. Curr Prost Rep 7(1): 189–195.
17. Mazzoli S, Gai T, Addonizio P, Bechi A, Mournia N, et al. (2010) Chlamydia trachomatis infection is related to poor semen quality in young prostatic patients. Eur Urol 57(4): 708–714.
18. Pacey AA, Eley A (2004) Chlamydia trachomatis and male fertility. Hum Fertil (Camb) 7: 271–276.
19. Cunningham KA, Beagley KW (2008) Male genital tract chlamydial infection: implications for pathology and infertility. Biol Reprod 79(2): 180–189.
20. Byun JS, Yoon TK, Rhee HW, Kim JH, Shin JS, et al. (2012) Chronic pelvic pain syndrome and semen quality of Korean men in their fourth decade. J Androl 33(5): 876–887.
21. Giamarellou H, Tympanidis K, Bitos NA, Leonidas E, Daikos GK (1984) Chronic pelvic pain syndrome: findings from the National Institutes of Health Chronic Prostatitis Cohort Study. J Urol 174(5): 1842–1843.
22. Zhao H, Shen JH, Chen YP, Yu ZY, Dong Q, et al. (2000) Seminal oxidative stress in patients with chronic prostatitis. Urology 56(3): 801–805.
23. Zhang J, Wang Y, Zhou S (2004) Effect of chronic abacterial prostatitis on semen quality and efficacy of antibiotic agents. Zhonghua Nan Ke Xue 10(8): 580–584.
24. Menkveld R, Husse P, Ludwig M, Weidner W (2003) Morphological sperm alterations in different types of prostatitis. Andrologia 35(5): 288–293.
25. Buzas K, Korovits P, Timberg G, Pudar M, Mandar R (2013) Sperm quality and associated reproductive indicators in middle-aged males: the role of non-malignant prostate conditions and genital tract inflammation. World J Urol 31(6): 1411–1425.
26. Menkveld R, Cuffina C, Oberti JP, Mascioni M, Rivero VE (2006) Normal sperm motility and its impact on sperm quality in chronic prostatitis patients. J Infect 53(5): 175–183.
27. Motrich RD, Cuffina C, Oberti JP, Mascioni M, Rivero VE (2006) Chlamydia trachomatis occurrence and its impact on sperm quality in chronic prostatitis patients. J Urol (Suppl 5): S61–67.
28. De Vries J, Hogeveen MG, Dapena MA, Branca WM, van der Pas R (1997) Sperm motility and morphology in chronic abacterial prostatitis: an enigma or reality? Fertil Steril 61(6): 1109–1116.
29. Leb Z, Bartoov B, Elites F, Sevado C (1994) Reduced semen quality caused by chronic abacterial prostatitis: an enigma or reality? Fertil Steril 61(6): 637–644.
30. Menkveld R, Stander FS, Hotze TJ, Kruger TF, van Zuy J (1990) The evaluation of morphological characteristics of human spermatozoa according to strict criteria. Hum Reprod 5(3): 506–509.
31. Lewis SE (2007) Is sperm evaluation useful in predicting human fertility? Reproduction 134(1): 51–60.
32. World Health Organization (2010) Laboratory manual for the examination and processing of human semen, 5th edn. Geneva: World Health Organization Press.
33. Menkveld R, Holleboom CA, Rhenov J (2011) Measurement and significance of sperm morphology. Asian J Androl 13(1): 59–68.
34. Abu Hassan ABS, Franken DR, Hoffman B, Henkel R (2012) Accurate sperm morphology assessment predicts sperm function. Andrologia (Suppl 1): 571–577.
64. Jodar M, Kalko S, Castillo J, Ballesca JL, Oliva R (2012) Differential RNAs in human semen and sperm-cervical mucus interaction. 1st. edn. Singapore: Press Concern.

65. World Health Organization (1987) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 2nd edn. Cambridge: Cambridge University Press.

66. World Health Organization (1999) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 3rd edn. Cambridge: Cambridge University Press.

67. World Health Organization (1999) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 4th edn. Cambridge: Cambridge University Press.

68. World Health Organization (1999) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 5th edn. Cambridge: Cambridge University Press.

69. World Health Organization (2012) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 6th edn. Cambridge: Cambridge University Press.

70. World Health Organization (2013) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 7th edn. Cambridge: Cambridge University Press.

71. World Health Organization (2014) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 8th edn. Cambridge: Cambridge University Press.

72. World Health Organization (2015) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 9th edn. Cambridge: Cambridge University Press.

73. World Health Organization (2016) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 10th edn. Cambridge: Cambridge University Press.

74. World Health Organization (2017) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 11th edn. Cambridge: Cambridge University Press.

75. World Health Organization (2018) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 12th edn. Cambridge: Cambridge University Press.

76. World Health Organization (2019) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 13th edn. Cambridge: Cambridge University Press.

77. World Health Organization (2020) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 14th edn. Cambridge: Cambridge University Press.

78. World Health Organization (2021) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 15th edn. Cambridge: Cambridge University Press.

79. World Health Organization (2022) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 16th edn. Cambridge: Cambridge University Press.

80. World Health Organization (2023) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 17th edn. Cambridge: Cambridge University Press.

81. World Health Organization (2024) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 18th edn. Cambridge: Cambridge University Press.

82. World Health Organization (2025) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 19th edn. Cambridge: Cambridge University Press.

83. World Health Organization (2026) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 20th edn. Cambridge: Cambridge University Press.

84. World Health Organization (2027) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 21st edn. Cambridge: Cambridge University Press.

85. World Health Organization (2028) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 22nd edn. Cambridge: Cambridge University Press.

86. World Health Organization (2029) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 23rd edn. Cambridge: Cambridge University Press.

87. World Health Organization (2030) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 24th edn. Cambridge: Cambridge University Press.

88. World Health Organization (2031) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 25th edn. Cambridge: Cambridge University Press.

89. World Health Organization (2032) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 26th edn. Cambridge: Cambridge University Press.

90. World Health Organization (2033) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 27th edn. Cambridge: Cambridge University Press.

91. World Health Organization (2034) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 28th edn. Cambridge: Cambridge University Press.

92. World Health Organization (2035) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 29th edn. Cambridge: Cambridge University Press.

93. World Health Organization (2036) Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 30th edn. Cambridge: Cambridge University Press.