Inflammatory Infertility

12

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12.1 Definition

Inflammatory infertility occurs when male infertility is provoked by inflammation of the urogenital tract and might constitute a curable cause of infertility [1]. About 10–15 % of infertile men have genital tract inflammation. After exclusion of urethritis and/or bladder infection, a sperm leukocyte concentration of $>10^6$/mL indicates inflammation [2]. It was recently advocated that a high leukocyte count in prostate-specific materials, even in the absence of clear leukocytospermia, may be associated with male infertility/dyspermia [3]. A concentration of $>10^3$ colony-forming units is significant for bacteriospermia [2].

Clinical studies raise doubts about whether inflammation of epididymis and didymis negatively affect male fertility when seminal duct obstruction is absent [4], leading to the suspicion that inflammation of the testicles exerts a poor influence on fertility. In fact, inflammation is one of the most important components of immune protection. On coming into contact with pathogen antigens, cells of the inflammatory response release signaling molecules (proinflammatory cytokines), which amplify the response by recruiting other macrophages and granulocytes to the infection site. To prevent inflammatory damage, another set of signaling molecules have the function of turning the signal off [5]. However, the disruption of immune response at the testicular level strongly affects spermatogenesis, indicating a protective role of the immune system in regard of fertility potential [6, 7].

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Further testicular macrophages play an important role in the balance between defense against invading microorganisms and "testicular immune privilege," which serves to protect the neoantigens of the meiotic and haploid germ cells that appear during puberty after the establishment of self-tolerance. Although testicular macrophages exhibit many typical macrophage characteristics such as effective antigen presentation, phagocytic functions, and expression of Fc receptors and major histocompatibility complex class II receptor [8], they are more reminiscent of a type-2 macrophage displaying diminished proinflammatory responses and reduced capacity to induce T-cell activation [9].

Thus the majority of the so-called inflammatory infertilities are of prostatic origin, with epididymitis of marginal interest.

12.2 Epididymitis

Acute epididymitis is divided into two classes [10, 11].

1. Sexually transmitted epididymitis (usually linked to urethritis), caused most often by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, occurs among sexually active adults younger than 35 years
2. Nonsexually transmitted epididymitis is often associated with urinary tract infections, and occurs more often in adults older than 35 or who have recently undergone urinary instrumentation procedures

A slight impairment of sperm forward motility might occur, which is completely recovered after appropriate antibiotic therapy [12]. Obstructive azoospermia after bilateral epididymitis can occur, although its prevalence is unknown.

12.3 Prostatitis

12.3.1 Definition and Categorization

Prostatitis is a prostatic inflammation. About half of all men suffer from prostatitis symptoms during their life span [13, 14]. Prostatitis is classified according to five categories: acute prostatitis (category I), chronic bacterial prostatitis (category II), abacterial inflammatory prostatitis (category IIIa), abacterial noninflammatory prostatitis (category IIIb), and asymptomatic prostatitis (category IV) [15].

Chronic prostatitis increases the risk for benign prostatic hyperplasia and prostate cancer [16, 17], and may affect male reproductive health [18].

12.3.2 Etiology of Prostatitis

Escherichia coli, *Klebsiella* sp., *Proteus mirabilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *C. trachomatis*, and *Ureaplasma urealiticum* are the most common bacteria involved in bacterial prostatitis infections. The route of infection is urinary ascending or lymphatic transrectal [19].

12.3.3 Pathogenesis of Dyspermia Associated with Prostatitis

Most of the literature agrees that the existence of bacteria in the prostate is linked with asthenospermia and decreased male reproductive health [20]. Chronic prostatitis seems to affect sperm count mainly if associated with irritable bowel syndrome, because of dilation of the periprostatic venous plexus and increased temperature [21]. An increase in reactive oxygen species (ROS) from leukocytes [22] has been indicated as a further physiopathologic mechanism of dyspermia associated with prostatitis.

12.3.4 Diagnosis

Although several symptomatic indices for prostatitis have been developed, only the National Institutes of Health (NIH) Chronic Prostatitis Collaborative Research Network has produced a valid instrument for evaluation of symptoms of prostatitis: the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). This index has nine items divided into three domains (pain, urinary symptoms, and quality of life), and is used as a tool for the diagnosis and follow-up of chronic prostatitis and chronic pelvic pain syndrome. Initially it was presented in English [23] (Table 12.1) and later also in Italian [24].

The prostate is tender, with various degrees of pain at objective examination. Urine culture and expressed prostatic secretion (EPS) represent the most important investigations for the diagnosis and categorization of prostatitis. EPS has been fully described by Mears and Stamey (Table 12.2) [25].

If prostatic biopsy is contraindicated [26], transrectal echography might be of some help when stones or abscess are suspected [27]. The efficacy of semen culture in the diagnosis and evaluation of chronic prostatitis remains unclear, and ejaculate culture is not recommended as a first line of diagnostic evaluation in these patients [28]. Increased seminal plasma elastase [1], interleukins (especially interleukin-6) [29], and ROS [1], in addition to decreased zinc, citric acid, fructose, phosphatase, and α-glutamyltransferase [30], are regarded as biochemical signs of chronic prostatitis.

Table 12.1 National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) [23]

Part a: National institutes of Health: classification system for prostatitis

Type		Classification	Definition
I		Acute bacterial prostatitis	Evidence of acute bacterial infection
II		Chronic bacterial prostatits	Evidence of recurrent bacterial infection
III	A	Chronic abacterial inflammatory prostatitis	White blood cells in semen, expressed prostatic secretions or VB3
	B	Chronic abacterial non-inflammatory prostatitis	No white blood cells in semen, expressed prostatic secretions or VB3
IV		Asymptomatic inflammatory prostatits	No symptoms, incidental diagnosis during prostate biopsy or presence of white blood cells in prostatic secretions during evaluation for others disorders.

Part b) NIH Chronic Prostatitis Symptom Index (NIH-CPSI).

Pain or discomfort.

1) In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a) Area between rectum and testicles (perineum)	1	0
b) Testicles	1	0
c) Tip of the penis (not related to urination)	1	0
d) Below your waist, in your pubic or bladder area	1	0

2) In the last week, have you experienced:

	Yes	No
a) Pain or burning during urination	1	0
b) Pain or discomfort during or after sexual climax (ejaculation)	1	0

3) How often have you had pain or discomfort in any of these areas over the last week?

0	Never
1	Rarely
2	Sometimes
3	Often
4	Usually
5	Always

4) Which number best describes your average pain or discomfort on the days that you had it, over the last week? 0 = no pain; 10 = pain as bad you can imagine.

0	1	2	3	4	5	6	7	8	9	10

Urination

5) How often have you had a sensation of not emptying your bladder completely after you finished urinating over the last week?

0	Not at all
1	Less than 1 time in 5
2	Less than half time
3	About half time

Table 12.1 (continued)

4	More than half time
5	Almost always

6) How often have you had to urinate again less than two hours after after you finished urinating over the last week?

0	Not at all
1	Less than 1 time in 5
2	Less than half time
3	About half time
4	More than half time
5	Almost always

Impact of symptoms

7) How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

0	None
1	Only a little
2	Some
3	A lot

8) How much did you think about your symptoms, over the last week?

0	None
1	Only a little
2	Some
3	A lot

Quality of life.

9) If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

0	Delighted
1	Pleased
2	Mostly satisfied
3	Mixed (about equally satisfied and dissatisfied)
4	Mostly dissatisfied
5	Unhappy
6	Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains.
Pain: Total of items 1, 2, 3 and 4 =……..
Urinary symptoms: Total of items 5 and 6 = ……
Quality of life impact: Total of items 7, 8 and 9……

Table 12.2 Mears and Stamey localization technique [25]

The test begins when the patient needs to void: drink 500 mL water, 30–60 min before the test
Four sterile containers are needed, named VB1, VB2, EPS, and VB3
Retract completely the foreskin
Cleanse the glans with sterile physiologic solution and dry the glans with sterile gauze
Urinate 10–20 mL in VB1
Urinate 200 mL in the toilet and without interrupting the stream urinate in VB2
The physician massages the prostate until several drops of prostatic secretion are obtained (EPS)
If no EPS could be collected during massage, a drop may be present at the orifice of urethra, and this drop should be taken with a 10-μL calibrated loop and cultured
Immediately after massage the patients urinates 10–15 mL in VB3

12.3.5 Therapy

A full review of the therapy of prostatitis is presented on the Web site of the European Urological Association (EUA): http://www.uroweb.org/guidelines/online-guidelines/?no_cache=1 It should be noted that trimethoprim-sulfamethoxazole is contraindicated for the treatment of inflammatory infertility linked to prostatitis because this drug is toxic for male gametes (see the Chap. 15). The therapy of prostatitis is mainly aimed at resolving the symptoms (see the following paragraph), and from a reproductive point of view the goals are reduction/eradication of microorganisms in prostatic secretions and semen, normalization of sperm inflammatory parameters, and improvement of sperm count [1, 14, 31]. At present only antibiotic therapy is achieving these goals [1].

12.3.6 Prognosis of Prostatitis in Terms of Human Fertility

EUA guidelines indicate that antibiotic treatment often eradicates microorganisms but cannot reverse anatomic dysfunctions, and might improve sperm quality, which does not necessarily enhance the probability of conception [4].

These data are not surprising, because the relationship between male fecundity and sperm count is hyperbolic and achieves a plateau at about 30×10^6 spermatozoa/mL, 50 % class A motility, and 14 % typical forms (strict criteria) [32–34]. Thus the more severe the dyspermia the more crucial is its therapy to improve couple fertility, and chronic prostatitis is seldom associated with severe dyspermia [4, 20, 21]. Furthermore, male fecundity is linked more to the quality of spermatogenesis than to sperm count [35, 36], and spermatogenesis is obviously not or poorly affected in the course of prostatitis. Despite these limitations to therapy, it is generally recognized that appropriate therapy for prostatitis should be performed to ensure, at the very least, symptom relief.

12.4 Mumps Orchitis

Mumps orchitis is rare; however, because of its detrimental sequelae on sperm count it merits discussion here. Orchitis is a common complication of mumps in postpubertal men affecting about 20–30 % of cases (10–30 % of which are bilateral), often results in testicular atrophy, and occurs 1–2 weeks after parotitis [37].

The causes of testicular atrophy are not fully known. In the course of inflammation the tunica albuginea forms a barrier against edema, and the subsequent rise in intratesticular pressure leads to pressure-induced testicular atrophy [38]. Adamopoulos et al. found elevated luteinizing hormone (LH) levels and an exaggerated pituitary response to LH-releasing hormone (LHRH) stimulation in the acute phase of mumps orchitis. Basal testosterone concentrations returned to normal after several months, whereas mean basal follicle-stimulating hormone (FSH) and LH concentrations remained significantly increased at 10 and 12 months after the acute phase [39].

Mumps orchitis rarely leads to azoospermia, more frequently leading to various degrees of dyspermia [40]. Testicular sperm extraction is indicated in cases of azoospermia (even with high concentrations of FSH and LH), whereas no treatment has been proposed for dyspermia [41].

12.5 Sperm DNA Fragmentation in Inflammatory Infertility: A Less Orthodox Point of View

Sperm DNA fragmentation (SDF) is the separation or breaking of DNA strands into pieces. Any form of DNA damage may result in male infertility. Sperm DNA integrity is essential for the complete transmission of genetic information, and is necessary for the normal fertilization and embryo growth in both natural and assisted conception [42, 43], but also for normal fetal development [44]. It has been reported that when 30 % or more of sperm DNA is damaged, natural pregnancy is not possible [45, 46]. Approximately 15 % of patients with male factor infertility have a normal semen analysis [47].

Increased sperm DNA fragmentation is frequently observed in males with normal semen characteristics. In fact, sperm DNA damage is found in 8 % of men with normal seminal parameters [48, 49]. Moreover, a significant proportion of males (8.4–23 %) diagnosed as unexplained infertile according to conventional semen analysis have high levels of sperm DNA fragmentation [50–53]. DNA integrity can be considered an effective monitor of normal male fertility potential [54].

High levels of sperm DNA fragmentation have been correlated with low fertility potential, failure to obtain blastocysts, hindrance in embryonic development, increased risk of recurrent miscarriages, reduced chances of successful implantation, and abnormal outcomes in the offspring [55–57].

Several etiologic factors have been associated with sperm DNA fragmentation: environmental conditions and cigarette smoking [58, 59], chemotherapy [60–62], irradiation [63, 64], cancer [65], varicocele [66, 67], leukocytospermia [68, 69], advanced paternal age [70–72], high fever [73], and chronic prostatitis [74–78]. Sharma et al. found the highest levels of ROS in semen of infertile men with prostatitis [79]. High levels of ROS mediate the DNA fragmentation commonly observed in spermatozoa of infertile men [80, 81]. Therefore, inflammations of the male genitourinary tract can adversely affect male fertility by causing sperm DNA damage.

Chronic prostatitis affects about 10–15 % of the male population [82]. In other studies the prevalence of prostatitis symptoms ranged from 2 to 9.7 % [83–85]. Prostatitis is the most frequent urologic diagnosis in males younger than 50 years [86]. It has been estimated that approximately 50 % of men will suffer from prostatitis during their lifetime [87]. A study of National Center for Health Statistics showed that about 25 % of outpatients evaluated for genitourinary problems suffered from prostatitis [88]. Males with a previous diagnosis of prostatitis had a 20–50 % risk for recurrent episodes [89]. A history of male genital inflammations, including prostatitis, epididymitis, and orchitis, occurs in 5–12 % of infertile men [90].

A study by El-Bayoumi et al. has revealed that prostatitis was the cause of infertility in 27.5 % of a sample of 375 infertile male patients [91]. A more recent study has shown chronic prostatitis as a cause of infertility in 39.1 % of 534 patients with male infertility [92].

Hu et al., in their recent (2013) study, have shown that chronic prostatitis significantly reduces sperm quality and male fertility, also highlighting a significant increase in sperm DNA fragmentation [76].

Considering that sperm DNA fragmentation is a frequent condition (due to various causes) and that chronic prostatitis is also very common and causes infertility in a high percentage of cases, one can deduce that sperm DNA damage is a frequent precondition for male infertility.

As sperm DNA fragmentation cannot be detected by routine molecular and cytogenetic methods, several assays have been developed to evaluate sperm chromatin/DNA integrity.

Some of these tests measure DNA damage directly, such as TUNEL (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling assay) and COMET (single-cell gel electrophoresis) [93, 94]. Other tests (indirect) include SCSA (sperm chromatin structure assay) and the SCD test (sperm chromatin dispersion) [95, 96]. The SCD test and TUNEL assay are both effective in detecting sperm DNA damage; however, using bright-field microscopy, the SCD test appears to be more sensitive than TUNEL [97]. Sperm DNA fragmentation has now become a new biomarker for male infertility diagnosis [98].

There are several notable facts regarding the interpretation and evaluation of the results of these different methods, as follows.

SCSA: The pregnancy rates are significantly higher with DNA fragmentation index (DFI) below the thresholds of 30–40 % [99]. Other investigators have found that a DFI cutoff level of 30.27 % was able to discriminate infertile and fertile men [100];

TUNEL: A threshold value of 20 % sperm DNA fragmentation (SDF) has been suggested to distinguish between fertile men and infertile patients [54]. A more recent study has shown a cutoff value of 19.2 % that can differentiate infertile men with DNA damage from healthy men [101];

COMET (alkaline test): The risk of failure to achieve a pregnancy increases when SDF exceeds a prognostic threshold value of 52 % [102];

COMET (neutral test): When SDF exceeds a prognostic threshold value of 77.5 %, there is a high risk of pregnancy failure [103];

SCD test: Men with SDF greater than a diagnostic threshold of 22.75 have a high risk of infertility [103].

According to current knowledge, intake of antioxidants may be beneficial in reducing sperm DNA damage, particularly in men with high levels of DNA fragmentation [104]. It is also important to identify behaviors that may reduce sperm DNA damage, such as removing testicular gonadotoxins and/or hyperthermia, treatment of genital tract infections and chronic prostatitis, correction of varicocele, smoking cessation, and reducing radiation exposure [80, 104–109].

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