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## INVITED COMMENTARY

Male Infertility

### ***Chlamydia trachomatis* infection of the male genital tract: what seems to be the trouble?**

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Male genital tract inflammation/infection and its impact on male fertility are still widely neglected in the workup of male fertility disturbances. Apart from inconsistent definitions of such inflammatory conditions which allow no adequate diagnosis and, consequently, no rational therapeutic approach, the role of bacterial infection, in particular by *Chlamydia trachomatis*, is also controversially discussed. One reason for that may be insufficient tools of sperm analysis in many laboratories that only rely on basic semen parameters as sperm number, motility, and morphology, in best cases accompanied by determination of the concentration of leukocytes. To make matters worse, the WHO (2010, WHO Manual for the examination and processing of human sperm, 5<sup>th</sup> Edition) recommended threshold of the latter – more than 1 million peroxidase positive leukocytes per ml for the definition of inflammation – is also not generally accepted, at least not within the group of experts in this field. Therefore, it seems mandatory to perform extended semen analysis including relevant sperm function tests, in order to estimate the impact on male fertility caused by inflammatory and infectious factors.<sup>1</sup> Against this background, the paper by Zhou *et al.*<sup>2</sup> on the effects of *C. trachomatis* infection on male fertility is highly appreciated.

In their retrospective study, a large cohort of 7154 infertile males were explored. 416 of them, around 5.8%, have turned out to be *C. trachomatis* positive – following pcr testing. In addition to determination of routine semen parameters, the concentration of granulocyte elastase in the seminal plasma as a marker of inflammation and acrosin activity as an important sperm function test relevant for sperm–egg interaction have been assessed. Moreover, antisperm antibodies as potential sequelae of inflammatory processes have been investigated by means of the mixed antiglobulin reaction (MAR) test. As compared to the control group, higher white blood cell count and higher concentrations of granulocyte elastase have been observed in the semen of *C. trachomatis*-infected patients reflecting an inflammatory response. However, apart from a lower semen volume, no further differences regarding routine semen parameters, acrosin activity, and antisperm antibodies have been encountered.

At first glance, these results seem relatively reassuring. However, some additional aspects should be considered and need further discussion, not least with respect to the necessity of treatment of *C. trachomatis*-infected patients with or without disturbed fertility.

Previously, it has several times been communicated that *C. trachomatis* infection is associated with disturbed DNA integrity, which enhances the probability of fertilization failure and may even lead to early pregnancy loss.<sup>3</sup> Unfortunately, this important sperm function parameter has not been investigated in the study discussed

here, although it would have provided valuable additional information in view of the large cohort examined.

A further aspect that is worth to be considered is that this kind of study – others have also been conducted – considers only the acute status of infection – as long as *C. trachomatis* is detected by pcr testing – but no information about ongoing, chronic inflammatory processes, initiated by the acute infection, after the causative agent has either been elucidated or is at least no longer detectable, is provided.

So far, it is not clear, whether *C. trachomatis* itself or the provoked inflammatory reaction causes detrimental effects on sperm quality. In the study by Zhou *et al.*<sup>2</sup> inflammatory signs in the semen of *C. trachomatis*-positive patients have been observed as well as measured by granulocyte elastase and the number of leukocytes; however, for better assessment of consequences of these findings results of pregnancy rates, following either natural conception or ART techniques would have been informative.

In men, *C. trachomatis* first infects the urethra, which usually may result in further episodes of chronic silent infection affecting prostate, seminal vesicles, epididymis, and even testis. Dysfunction of prostate and seminal vesicles most probably has contributed to the lower semen volume observed in the discussed study rather than obstructive processes which are unlikely in such an early state on infection/inflammation.

As already mentioned, *C. trachomatis* infection may lead to persistent, long-term, subclinical infections. After bacterial recognition, a subset of pro-inflammatory cytokines and chemokines are continuously released by epithelial cells. In addition, this pathogen can efficiently infect and replicate into human dendritic cells, leading to the production of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, IL-18, and TNF $\alpha$ . In several studies, it has been demonstrated that elevated concentrations of such cytokines have been closely correlated with impaired semen parameters and, in particular – with disturbed DNA integrity.<sup>4,5</sup> Bacterial infections may disturb male fertility by different mechanisms. Acute infection can lead to structural defects of spermatozoa, and thus interfere with important sperm functions like motility, sperm-egg-binding, or DNA integrity, amongst others. But, what has also be taken into account, are long-term effects of inflammatory processes, risen by the acute bacterial infection, once the causative agents have been eliminated, or, are no longer detectable. Here can come into play some further aspects have to be considered. Chronic, ongoing infections or sequelae of acute infections are frequently torpid and don't cause any physical symptoms in most cases. However, they are usually accompanied by a higher number of leukocytes, in particular the occurrence of macrophages has to be regarded, as well as increased concentrations of pro-inflammatory cytokines like IL-6, IL-8, TNF-alpha, and, not least high concentrations of reactive oxygen species can be measured. All these factors have been demonstrated to be deleterious to sperm morphology and sperm functions as mentioned above. For these reasons, considering only a lower seminal volume, which is most likely due to an additional dysfunction of prostate and seminal vesicles is insufficient, as the most harmful affections of genital tract inflammations take place in

the testicles and epididymis.<sup>1</sup> Thus, acute as well chronic infections/inflammations may hamper the induction of a pregnancy, following either natural conception or ART techniques. Therefore, information about pregnancy rates in the study discussed here, would have been informative.

In view of these considerations, an ideal study would investigate not only the impact of more or less acute infection with *C. trachomatis*, based on PCR testing, but also long-term effects after several months. However, after all, we already know about the role of *C. trachomatis* infection in male fertility, this may be a rather unethical approach. Therefore, immediate treatment with antibiotics in cases of *C. trachomatis* infection is recommended, in symptomatic as well asymptomatic men, not least with respect to probability of sexual transmission to the female partner with all the negative consequences for female fertility. In addition, concomitant treatment with antiphlogistics or corticosteroids may be considered in order to prevent the long-term effects of chronic inflammation on the male genital tract and sperm DNA integrity. Such an approach has several times been proposed.<sup>1</sup>

#### COMPETING INTERESTS

Both authors declare no competing interests.

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