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## ORIGINAL ARTICLE

# Low sperm counts in genitourinary medicine clinic attendees: results from a case—control study

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Accepted 6 April 2012

Published Online First  
6 December 2012

## ABSTRACT

**Objectives** To conduct a case—control study of abnormalities in the semen of genitourinary (GU) medicine clinic attendees compared with general practice (GP) controls and in patients with asymptomatic and symptomatic non-specific urethritis (NSU) before and after the urethritis resolves.

**Methods** Rates of semen abnormalities were compared between the different groups (19 with symptomatic and 27 with asymptomatic NSU, seven with symptomatic non-NSU and 64 clinic controls) and between clinic attendees and 417 patients attending GP for the first investigation of possible infertility. Those with symptomatic or asymptomatic NSU gave repeat semen samples on resolution of the NSU.

**Results** The study included 117 clinic volunteers. They were shown to have statistically significantly worse total sperm counts ( $p=0.002$ ), volume of semen ( $p<0.001$ ) and percentage of abnormal forms ( $p<0.04$ ) compared with 417 GP controls. Compared with the rest of the clinic volunteers, asymptomatic NSU patients had statistically significantly lower total sperm counts ( $p<0.02$ ). Asymptomatic NSU patients had statistically significantly lower total sperm counts compared with symptomatic NSU patients ( $p<0.02$ ). Compared with GP controls, clinic controls had statistically significantly inferior total sperm counts ( $p=0.009$ ) and semen volume ( $p<0.001$ ).

**Conclusions** GU clinic attendees are more likely to have abnormalities of semen than patients attending GP for the first check for possible infertility. A high rate of abnormal semen findings are found in patients with and without NSU but the highest rate occurred in those with asymptomatic NSU. Is asymptomatic NSU therefore pathogenic and does it require treatment like symptomatic NSU?

## INTRODUCTION

In developed countries, 22% of infertility is caused by a male factor alone and in a further 21% both male and female factors are involved.<sup>1</sup> Subfertility affects one in 20 men.<sup>2</sup> Known causes of male subfertility are genital tract infection (epididymitis and orchitis), testicular disease and abnormalities, systemic disease and external factors, for example, drugs.<sup>2</sup> Male subfertility is rarely caused by endocrine deficiency.<sup>2</sup> The evidence linking environmental factors and impaired human fertility is weak.<sup>3</sup>

Epididymitis, a recognised cause of male infertility,<sup>2</sup> is a common complication of urethritis. In

genitourinary (GU) medicine clinics in the UK, cases of non-chlamydial/non-gonococcal (non-specific) epididymitis are seven times as common as those associated with *Chlamydia trachomatis*.<sup>4</sup> It is well recognised that *C trachomatis* infection in women can cause infertility following a symptomatic pelvic infection or asymptotically without a clinically apparent salpingitis.<sup>5</sup> Although it is known that symptomatic epididymitis can cause male infertility,<sup>2</sup> there is no clear in vivo evidence that asymptomatic non-chlamydial urogenital infection can have an adverse effect on male fertility.<sup>6</sup>

The findings of an epidemiological study suggested an association between infection with *C trachomatis* (CT) in men and unexplained infertility and implied that infection was frequently asymptomatic.<sup>7</sup> CT has been found to be asymptomatic in around 50% or more cases in community and clinic settings in the UK and in a rural setting in Tanzania.<sup>8–10</sup>

In vitro work suggests that male genital tract infections may adversely affect sperm quality and fertilising potential by a variety of mechanisms, for example, infection-related impairment of accessory gland function, partial or full obstruction of sperm transport, infection-related disruption of the blood-testis barrier inducing the generation of anti-sperm antibodies, and so on.<sup>11</sup>

The diagnosis of non-specific urethritis (NSU) (non-chlamydial and non-gonococcal) is made on microscopy. The latest guideline from the British Association for Sexual Health and HIV has changed former guidance so that screening for asymptomatic NSU and checking for unresolved asymptomatic NSU after treatment of symptomatic NSU are no longer advocated.<sup>12</sup> However, other clinicians have advocated caution in adopting such policies before further research has been done.<sup>13</sup> This study examines fertility in men with NSU, that is, negative for both *Neisseria gonorrhoeae* (NG) and CT, and other clinic attendees. Primary aims were to investigate whether there is a higher incidence of abnormalities in the semen of men with urethritis compared with controls and second to investigate whether any abnormalities found in the semen of men with urethritis are corrected when the urethritis resolves. A secondary aim was to investigate whether asymptomatic urethritis has similar effects (if any) on semen to symptomatic urethritis. The hypothesis was that just as infertility may be caused by either symptomatic or asymptomatic infection in women, so the same may occur in men.

## METHODS

### Study population

Male genitourinary clinic attendees aged 16 years and over were invited to participate in the study. They were recruited between March 2006 and February 2010 and were required to give signed written consent. Follow-up finished in September 2010. Ethics approval was granted by the Peterborough and Fenland Local Research Ethics Committee. The study took place in the Department of Genitourinary Medicine at Addenbrookes Hospital.

Inclusion criteria were patients who had ejaculated at some time in the previous week but not in the 48 h before the study sample and had held their urine for at least 3 h. Exclusion criteria were those aged under 16 years and patients found on questionnaire to have a known or suggested cause of male infertility.

These comprised prescription and recreational drugs known to cause male infertility, a history of testicular disease or abnormality or intrascrotal surgery, epididymitis or orchitis, or influenza or other serious illness in the previous 3 months. As patients with symptoms suggestive of possible prostatitis were not included, neither prostatitis questionnaires nor Meares–Stamey tests were used. Patients found to have *C trachomatis* were excluded from the analysis.

Patients were defined as having urethritis based on the analysis of a urethral smear according to the Giessen urethritis protocol, where there is evidence of >4 granulocytes per microscopic field (1000×).<sup>14</sup> Patients were divided into symptomatic (dysuria and/or urethral discharge) or asymptomatic (entirely free of symptoms). Clinic controls were asymptomatic men seeking a sexual health screen whose urethral smear showed that they did not have urethritis. It proved impossible to recruit a community control group. Therefore, a comparator group was formed from data collected by the Addenbrookes Hospital Cytology department on 417 patients attending general practice (GP) requesting a first check for possible infertility between January and October 2006 (referred to as GP controls). The same eligibility criteria for semen analysis applied, although this could not be checked by the study authors. A further small group comprised patients with dysuria and/or discharge who were negative for NGU on an early morning smear.

### Tests and questionnaire

Patients and clinic controls were required to hold their urine for at least 3 h before the urethra was swabbed. The study started before first pass urine samples had largely supplanted urethral swabs for chlamydia.

Each participant was required to answer questions to enable the doctor to complete a research questionnaire covering known and suggested determinants of male factor infertility.<sup>2,7</sup> Patients found on questionnaire to have a known or suggested cause of male infertility were excluded (see Introduction section).

Participants also underwent a screen for sexually transmitted infections as indicated by their clinical presentation and wishes. These tests included a urethral smear (as above), a urethral swab for culture for *N gonorrhoeae* and a urethral swab for PCR for *C trachomatis*.

Participants were also invited to produce a semen sample in the clinic after the consultation prior to starting their course of antibiotics (if appropriate). All patients found to have NGU were treated with Azithromycin 1 g oral stat. All patients were asked to return at 2 weeks to receive the results of their tests. Those who had presented with NGU had a repeat urethral

smear for quantitation of pus cells. Those with NSU also gave a repeat semen sample on resolution of their urethritis. Semen analysis was conducted according to the routine protocol.<sup>15</sup> NSU patients were also invited to return  $\geq 3$  months after diagnosis for a further semen sample.

### Data analysis

Data analysis was performed with the following tests: Kruskal–Wallis to compare the four separate groups of clinic volunteers in respect of age and semen findings; Fisher's exact as above for alcohol consumption and ethnic origin; Mann–Whitney U (MWU) to compare semen findings in the different patient groups;  $\chi^2$  for percentage of abnormal forms and percentage of non-progressors, McNemar's and the sign test for comparisons before and after treatment and standard non-parametric tests using SPSS (V.17.0; SPSS Inc).

## RESULTS

One hundred and fifty-one clinic volunteers were recruited to the study. Thirty-four of these patients were subsequently found to have *C trachomatis* and were therefore excluded from this analysis, leaving 117 patients whose data are presented here (data incomplete for one patient). These comprised 27 patients with asymptomatic NSU, 19 patients with symptomatic NSU, 64 clinic controls and seven patients who, despite symptoms of dysuria and/or discharge, were shown not to have NSU. In addition, the GP control group described above comprised 417 patients (data incomplete for one patient).

### Results of tests at presentation

There were no significant differences between the four clinic groups in respect of age, excessive alcohol consumption (>28 units/week), ethnic origin (83 Caucasian and 33 non-Caucasian) and current smoking habit (table 1). There was a statistical difference between the four groups in respect of having a history of sexually transmitted infections, with the group of symptomatic non-NSU patients having the highest rate,  $p=0.007$  on MWU (StatXact software; Cytel, Cambridge, Massachusetts, UK). The overall prevalence of smoking, 34/116, 29% (95% CI 21.0% to 37.6%), compares with 22% among men in the UK in 2009.<sup>16</sup>

The population of the above clinic volunteers were shown to have statistically significantly worse total sperm counts and volume of semen compared with GP controls,  $p=0.002$  and  $p<0.001$ , respectively, on MWU. The finding for percentage of abnormal forms of  $p=0.04$  is not thought to be significant, given the large number of analyses performed. There were no significant differences in respect of motility, sperm concentration and percentage of non-progressors (table 2). The total sperm counts in the five different groups are shown in the figure 1.

Of the GP controls, 68/416 (16.3%) had low sperm counts (<39 million) compared with 28/117 (23.9%) of clinic

**Table 1** Demographic features of clinic attendees

	Controls (n = 63)	Asymptomatic NSU (n = 19)	Symptomatic NSU (n = 27)	Symptomatic non-NSU (n = 7)
Age, mean (SD)	27.6 (7.1)	26.7 (7.4)	28.7 (5.8)	25.9 (5.2)
Smoker (%)	25	33	42	14
Excess alcohol (%)	24	19	16	14
Ethnicity white (%)	73	70	84	57
No history of STI	64	52	42	14

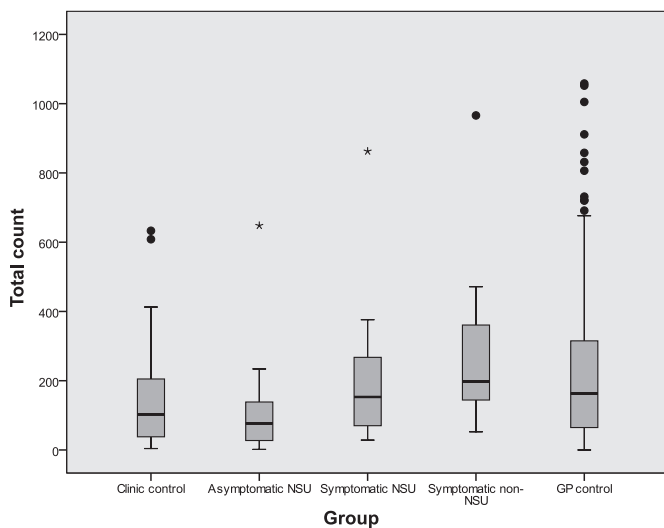
NSU, non-specific urethritis; STI, sexually transmitted infection.

**Table 2** Volume, sperm count and motility in clinic volunteers and GP controls

	N (missing), N = 534	Quartiles			MWU p Value
		25	50	75	
<b>Volume</b>					
GU clinic	117 (0)	1.8	2.4	3.4	<0.001
GP	417 (0)	2.2	3.2	4.4	
<b>Sperm count</b>					
GU clinic	117 (0)	47	108	200	0.002
GP	416 (1)	83	178	328	
<b>Motility</b>					
GU clinic	117 (0)	61	72	81	0.55
GP	398 (19)	63	74	80	
<b>Sperm concentration</b>					
GU clinic	117 (0)	22	49	88	0.25
GP	417 (0)	32	60	94	
<b>Percentage of abnormal forms</b>					
GU clinic	117 (0)	86	88	89	0.04
GP	417 (0)	86	87	89	
<b>Percentage of non-progressors</b>					
GU clinic	117 (0)	12	19	26	0.56
GP	417 (0)	13	19	25	

Volume in millilitres, total sperm count in millions, motility as percentage and sperm concentration as number per millilitre.  
 GP, general practice; GU, genitourinary; N, number of patients (varies in GP group because of non-suitability of some specimens); MWU, Mann-Whitney U test.

volunteers, Fisher's exact  $p=0.076$ , with an OR (95% CI) of 1.61 (0.98 to 2.65). This observed difference corresponded to a standardised difference of 0.33 and a post hoc power calculation confirmed that sample sizes were adequate after allowing both for multiple outcomes (by using 0.01 level of significance) and an imbalanced ratio of GP controls to clinic attendees (taken as four). The power to detect an effect size characterised by a standardised difference of 0.33 is just over 80% when using the sample sizes of 400 versus 100, both somewhat below actual sample sizes employed in this study. Results are as follows when different thresholds are used. For instance, using above and below 100 million, the rates were GU 49.6% versus GP 34.1%,



**Figure 1** Total sperm counts in all groups in study. Number of clinic controls = 64, asymptomatic non-specific urethritis (NSU) = 27, symptomatic NSU = 19, symptomatic non-NSU = 7, general practice (GP) controls = 417. Total sperm count in millions. Circles, outliers (>1.5 IQRs above 75th percentile). Stars, most extreme outliers.

$p=0.003$ , OR 1.90 (1.25 to 2.87). Using a cut-point of 200 million, corresponding figures were 75.2% versus 57.9%,  $p=0.001$ , OR 2.20 (1.39 to 3.50). The total sperm counts in the different groups are shown in the figure 1. There were no statistical differences between these groups when comparing sperm concentration, motility or percentage of non-progressors.

Examining the four separate groups of volunteers (symptomatic NSU, asymptomatic NSU, clinic controls and symptomatic non-NSU patients), there was a statistical differences in total sperm counts between the four groups,  $p=0.015$  on Kruskal-Wallis (table 3). There were no statistical differences between these groups when comparing volume, percentage of sperm concentration, motility, abnormal forms, percentage of non-progressors and white blood cells (Leucoscreen Test, performed in the 25 patients with five or more round cells per millilitre). Overall, 28/117 (23.9%) clinic volunteers had low sperm counts (<39 million): 9/27 asymptomatic NSU, 3/19 symptomatic NSU, 16/64 clinic controls and 0/7 symptomatic non-NSU patients.

Compared with the rest of the clinic volunteers, asymptomatic NSU patients had statistically significantly lower total sperm counts ( $p<0.02$ ) on MWU but not significantly lower volumes, sperm concentration, motility, percentage of abnormal forms or percentage of non-progressors.

Asymptomatic NSU patients had statistically significantly lower total sperm counts compared with symptomatic NSU

**Table 3** Volume, sperm count and motility in the four groups of clinic volunteers

	N	Quartiles			K-W/ $\chi^2$ p Value
		25	50	75	
<b>Volume</b>					
Controls	64	1.7	2.4	3.3	0.29
Asymptomatic NSU	27	1.4	2.0	3.2	
Symptomatic NSU	19	2.1	3.0	3.7	
Symptomatic non-NSU	7	2.2	2.4	3.4	
<b>Sperm count</b>					
Controls	64	45	108	205	0.015
Asymptomatic NSU	27	33	77	143	
Symptomatic NSU	19	70	153	267	
Symptomatic non-NSU	7	144	198	361	
<b>Motility</b>					
Controls	64	58	72	80	0.11
Asymptomatic NSU	27	64	72	81	
Symptomatic NSU	19	55	67	82	
Symptomatic non-NSU	7	79	81	83	
<b>Sperm concentration</b>					
Controls	64	21	49	85	0.11
Asymptomatic NSU	27	13	37	60	
Symptomatic NSU	19	20	47	121	
Symptomatic non-NSU	7	51	83	114	
<b>Percentage of abnormal forms</b>					
Controls	64	86	88	89	0.18
Asymptomatic NSU	27	87	88	89	
Symptomatic NSU	19	87	89	90	
Symptomatic non-NSU	7	86	87	87	
<b>Percentage of non-progressors</b>					
Controls	64	15	19	27	0.41
Asymptomatic NSU	27	12	20	27	
Symptomatic NSU	19	10	16	21	
Symptomatic non-NSU	7	7	16	27	

Volume in millilitres, total sperm count in millions, motility as percentage and sperm concentration as number per millilitre.  
 NSU, non-specific urethritis; N, number of patients; K-W, Kruskal-Wallis test, used for top four parameters;  $\chi^2$ , used for bottom two parameters.



patients ( $p < 0.02$ ) on MWU but no differences in volume, sperm concentration, motility, percentage of abnormal forms or percentage of non-progressors.

Compared with GP controls, clinic controls had statistically significantly inferior total sperm counts ( $p = 0.009$ ) and volume ( $p < 0.001$ ) on MWU but not sperm concentration, motility, percentage of abnormal forms or percentage of non-progressors.

### Results of follow-up tests

Thirty-eight patients with NSU (17 asymptomatic and 21 symptomatic) returned for at least one follow-up test (38/42, 83%). Comparisons were made between the various parameters in semen obtained at the first and last visits. The median time interval between the first and last semen specimens was 86 days (IQR = 100 days).

Twelve of the 38 (three symptomatic and nine asymptomatic) had low total sperm counts at presentation. Eleven of these counts improved at follow-up ( $p = 0.003$  on sign test). Eight of these achieved counts within the normal range.

McNemar's test on all 38 patients with NSU with repeat data shows no significant difference in whether or not the total counts were above or below the lower limit of normal (39 million) comparing semen at presentation and following resolution of the urethritis ( $p = 0.581$ ). Neither were there significant differences in the other parameters compared.

### DISCUSSION

Genitourinary (GU) medicine clinic attendees have been shown in this study to have statistically significantly inferior sperm counts, semen volume and percentage of abnormal forms compared with patients attending GP requesting a first check for possible infertility. This may be interpreted as showing that clinic attendees are more likely than the general population to carry organisms asymptotically and that such organisms are potentially damaging to male fertility. These are organisms that are hitherto unknown or not tested for in routine practice. GU clinic attendees are known to be at high risk of carrying pathogens asymptotically, for example, 43% of women attending this GU clinic were shown to have oncogenic human papillomavirus.<sup>17</sup> The decision to use the GP controls was taken after it was realised that the clinic controls had a high rate of semen abnormalities, and our attempts to recruit a community control group had failed.

Second, patients with asymptomatic NSU have statistically significantly lower sperm counts compared with the rest of the clinic volunteers and when compared with patients with symptomatic NSU. The explanation for this may be as follows. Patients with NSU carry organisms that can cause inflammation. If such a patient has symptoms, he is likely to present more quickly to a GU clinic than a patient with NSU who does not have symptoms. Therefore, organisms in the latter group will often have more time to damage the production of semen.

Third, even the seemingly normal clinic controls have lower sperm counts and semen volume than the GP controls. If asymptomatic organisms are the cause of the semen abnormalities in other clinic attendees and it is known that patients attending GU clinics are at high risk of harbouring pathogens asymptotically, this may be interpreted as showing that clinic controls, with no symptoms or signs suggestive of infection, nevertheless are more likely to have organisms with the capacity to damage semen.

There is some evidence to indicate that *C trachomatis* infection can affect sperm quality and sperm function<sup>18</sup> including, in vitro studies that show that co-incubation of spermatozoa with *C*

*trachomatis* causes a significant decline in numbers of motile sperm and results in premature sperm death.<sup>19</sup>

In a large study, Mazzoli *et al*<sup>20</sup> found strong associations in men with CT-positive prostatitis and low values for sperm concentration, percentage of motile sperm and normal morphological forms together with evidence for probable immunomediated damage to germinal cells. The same group had previously found anti-*C trachomatis* mucosal IgA in a high percentage of patients with prostatitis, suggesting that this organism could be causal in some cases.<sup>21</sup>

*Ureaplasma biovar 2* (formerly *Ureaplasma urealyticum*), frequently found in the urethra, has been shown to damage spermatozoa.<sup>22–23</sup> *Mycoplasma genitalium*, a common cause of urethritis,<sup>24</sup> can cause immobility of spermatozoa in vitro.<sup>25</sup> *N gonorrhoeae* is a less common cause of urethritis in the UK,<sup>24</sup> and although biologically plausible, it is currently unclear whether it can cause male factor infertility.<sup>26</sup> An uncommon cause of urethritis, *Trichomonas vaginalis*, has been linked with male factor infertility.<sup>27</sup>

Recognised causes of NGU such as *C trachomatis* and *M genitalium* are known to cause asymptomatic infection at times. One study found this to be the case in 60% of cases of *C trachomatis* urethritis and 27% of urethritis caused by *M genitalium*.<sup>28</sup>

Finally, almost all the NSU patients with low sperm counts improved following treatment. On the other hand, those with normal counts did not increase. There are two possible explanations. This may merely represent regression to the mean of statistical outliers. Alternatively, it may be argued that those with normal counts have not had damage by organisms and therefore treatment of those organisms would not be expected to produce an increase. Only further research can clarify this issue.

In male fertility in general, the results of antibiotic treatment have been disappointing. Individual agents within each of the major classes of antibiotics have been shown to have significant adverse effects on spermatogenesis or spermatozoal function in mammals.<sup>29</sup> Tetracycline, chloroquine, erythromycin and co-trimoxazole considerably impair sperm movement characteristics and significantly reduce sperm viability in vitro.<sup>30</sup> Amoxicillin appears to have negligible effect.<sup>30</sup> Furthermore, a controlled trial showed no benefit on semen quality from the use of erythromycin.<sup>31</sup> The patients attending GU clinics, with or without NSU, may, however, be a special case, given that their semen abnormalities are often likely to be caused by infection and therefore abnormalities may be more likely to improve with antibiotics.

In this study, the timing of the semen sample after previous ejaculation was asked routinely of clinic volunteers and those not meeting the accepted criteria were not invited to join the study. A possible weakness of the study is that it cannot be known whether the GP comparator group included some who did not meet these criteria. However, if so, such patients would be expected to have had lower quality semen as a result. This would have had the effect of reducing the apparent differences in semen between clinic volunteers and GP Controls. It is possible therefore that the differences demonstrated in this study between clinic and GP attendees would have been even greater if the guidance on timing of the samples had always been strictly adhered to by GP controls. Furthermore, if it had been possible to recruit a genuine cross-section of the general public, it is presumed that the differences would be substantially greater. The authors expect that the results could be generalised to other populations attending Sexual Health clinics.

The findings of this study raise several questions. First, is the carriage of unknown organisms responsible for the high rate of

## Key messages

- ▶ GU clinic attendees are more likely to have abnormalities of semen than patients attending GP for a first check for possible infertility.
- ▶ High rates of abnormal semen findings are found in patients with and without NSU but the highest rate occurred in those with asymptomatic NSU.
- ▶ The question of whether or not antibiotic treatment improves low sperm counts in patients with NSU requires further research.

various semen abnormalities found in GU clinic attendees? Second, does the finding that, among clinic attendees, patients with asymptomatic NSU are most likely to have low sperm counts imply that this condition is pathogenic and, like symptomatic NSU, therefore requires treatment? Third, is the high rate of semen abnormalities in clinic controls indicative of the silent carriage of unknown organisms in some attendees in this group? This study also points to the need for further research, in particular to resolve whether or not antibiotic treatment improves low sperm counts in patients with NSU.

**Acknowledgements** The authors thank Hamid Jalal, Tom Fanshawe, Chris Sonnex, Susie Forster, Andrew Prentice, Raj Mathur and Sandy Paget for their help in planning the project. Raj Mathur for commenting on a draft of the paper. Julia Burdett and Joanne Gibbs for their help in recruiting volunteers.

**Contributors** Roles of authors CAC: design of project, recruitment of patients, completion of clinical questionnaires, analysis of results; principal writer SC: design of project, cytological examinations and creation of cytological spreadsheet; co-writer CP: statistical analysis; co-writer OG: cytological examinations; co-writer SB: completion of clinical questionnaires and creation of spreadsheet; co-writer RW: cytological examinations; co-writer AG-M: completion of clinical questionnaires and creation of clinical spreadsheet; co-writer MO'D: design of project and co-writer.

**Competing interests** None.

**Ethics approval** Ethics approval was provided by Peterborough and Fenland LREC.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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