

History of febrile illness and variation in semen quality

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BACKGROUND: The purpose of this study was to analyse the effect of a history of febrile illness on semen quality. **METHODS:** Twenty-seven healthy men (median age 24.4 years) were followed with monthly semen samples and a daily record of the occurrence of experienced febrile episodes over a 16 month period between March 1998 and June 1999 in Copenhagen, Denmark. Semen samples were analysed for semen volume, sperm concentration, percentage immotile sperm and percentage morphologically normal sperm. **RESULTS:** Sperm concentration significantly decreased by 32.6% (95% confidence interval –49.9; –9.2) following fever during meiosis and by 35.0% (–50.5; –14.6) following fever during the postmeiotic period of spermatogenesis (spermiogenesis). The percentage of morphologically normal sperm was decreased by 7.4% (–11.6; –3.0) and the percentage of immotile sperm was increased by 20.4% (6.0; 36.8) by fever during spermiogenesis. The number of days the men experienced fever significantly affected their semen parameters. Thus fever during meiosis and spermiogenesis reduced sperm concentration with respectively 7.1% (–12.9; –0.9) and 8.5% (–13.6; –3.0) per day of fever. The percentage of morphologically normal sperm decreased 1.6% (–2.5; –0.6) and the percentage of immotile sperm increased 4.5% (1.7; 7.3) per day of fever during spermiogenesis. There was, however, a large variation in the individual response to fever. **CONCLUSIONS:** Sperm concentration, morphology and motility in a semen sample are adversely affected by a febrile episode during the postmeiotic period of spermatogenesis (spermiogenesis). Sperm concentration was also adversely affected by fever during the period of meiosis, whereas fever at other time points during spermatogenesis did not seem to significantly affect these sperm parameters. The adverse effect seemed to be dependent upon the number of days with fever.

Key words: fever/semen quality/spermatogenesis/variation

Introduction

It has several times been stated in publications and textbooks that it is a well-known phenomenon that semen quality can be affected by febrile illness. However, only few casuistic publications in semen donors (MacLeod and Hotchkiss, 1941; MacLeod, 1951; Buch and Havlovec, 1991) and patients with malignant or endemic febrile diseases (French *et al.*, 1973) have data to support this statement. Other publications have analysed the effect of temperature on semen quality in occupational studies (Thonneau *et al.*, 1998) and in studies on temperature regulation in the scrotum with inconclusive results, although many of the studies seem to indicate that high scrotal temperature is associated with decreased sperm concentration (Brown-Woodman *et al.*, 1984; Mieusset and Bujan, 1995). Some studies have also found an increase in the percentage abnormal sperm (MacLeod, 1951; French *et al.*, 1973) and in the percentage of immotile sperm (MacLeod, 1951) due to increased temperature. Animal studies have suggested that the pachytene spermatocytes and the early spermatids are the germ cells most sensitive to heat

(Chowdhury and Steinberger, 1970; Waites, 1991; Lue *et al.*, 1999) although heat also appeared to affect testicular mass and number of spermatogonia (Setchell *et al.*, 2001).

We report here the results of a prospective longitudinal study in healthy young men on the effect on semen parameters of reported fever at different time-intervals prior to semen sampling.

Materials and methods

Twenty-seven healthy men (median age 24.4 years) with no history of urogenital operations were followed from March 1998 until June 1999. During this period, they delivered a monthly semen sample and kept a daily record regarding the occurrence of experienced febrile episodes. The men were not requested to measure their body temperature, thus reported experienced febrile episodes were not in all cases verified by a body temperature measurement. An abstinence time of ≥ 2 days was requested but all semen samples were accepted regardless of duration of abstinence and the actual time was recorded. Semen samples were analysed according to the World Health Organization (1992) guidelines with modifications according to

Jørgensen *et al.* (1997). Sperm concentration and motility were analysed by six technicians, of which one analysed almost 50% of the samples. Sperm morphology was in all samples analysed by the same technician. The local ethics committee approved the study, and all men participated after informed consent.

Classification of phases in spermatogenesis

Spermatogenesis can be divided into four phases, i.e. mitotic proliferation, meiotic division, spermiogenesis (postmeiotic period) and epididymal sperm maturation, which occur approximately 57–80, 33–56, 9–32 and 0–8 days respectively prior to ejaculation of the sperm (Heller and Clermont, 1964) (Figure 1). Consequently, we used these time-intervals for our calculations.

Statistical analysis

Semen parameters—sperm concentration ($\times 10^6/\text{ml}$), sperm motility (percentage immotile sperm), sperm morphology (percentage normal sperm), or semen volume—were natural logarithm-transformed in order to obtain an approximate variance homogeneity and a normal distribution. To investigate the effect of fever during the different phases of spermatogenesis we used, for each semen parameter, a general linear model analysing all semen samples from all the men in one statistical model. This allowed adjusting for duration of abstinence, technician variation, and the inter-individual variation—the latter by having each subject entering the model as a random factor. As all semen samples from each man were used for the analysis, each man served as his own control, which is important when estimating the effect of febrile episodes. The effect of febrile episodes on these semen parameters was estimated for both +/- fever during 0–8, 9–32, 33–56 and 57–80 days before ejaculation, and as a linear effect in the number of days of fever. Each technician was allowed an individual level in the model, which adjusts for possible general differences between technicians. The effects of duration of abstinence were modelled using a piecewise linear function with one slope from 0 to 4 days of abstinence and another slope after 4 days. The Statistical

Package for the Social Sciences for Windows, edition 10.0.7 was used for the analysis.

Results

The men delivered between 11 and 17 semen samples each (median 16), and in total 419 semen samples. The median sperm concentration in the first 11 semen samples (delivered by all 27 men) was $74.5 \times 10^6/\text{ml}$ (range $1\text{--}370 \times 10^6/\text{ml}$). In the same semen samples the corresponding values for percentage normal sperm and percentage immotile sperm were 39.0% (22.0–59.0) and 34.6% (12.3–99.3) respectively. The median abstinence time was 57.8 h (range 2–273 h). In all, 15 (56%) of the 27 men experienced one or more episodes of reported fever during the study period (Table I). The febrile incidences lasted from 1 to 11 days (median 5). We found a significant adverse effect on semen quality of reported fever prior to semen sampling. To evaluate this in more detail we looked at the effect of fever and the number of days with fever during different time-intervals prior to a semen sample corresponding to the different phases in spermatogenesis as outlined in Materials and methods and Figure 1.

The percentage of semen samples produced following fever on the 57–80 (mitotic proliferation), 33–56 (meiosis), 9–32 (spermiogenesis) and 0–8 (maturation) days prior to ejaculation were 5.3, 4.7, 5.3 and 1.8 respectively. Table II shows the changes in semen parameters by fever at the different phases of spermatogenesis. Sperm concentration decreased by mean 32.6% if fever had occurred during the period when the ejaculated sperm were going through meiotic division, and a similar decrease (35%) was caused if fever had occurred during the period when the ejaculated sperm were going through spermiogenesis. The percentage of morphologically normal sperm decreased by 7.4% if the febrile episode occurred when the ejaculated sperm were going through spermiogenesis and the percentage of immotile sperm increased 20.4% by fever during the same period. Fever that had occurred at other time-

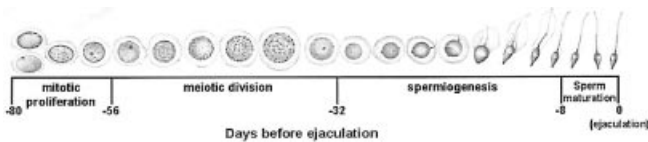


Figure 1. Schematic drawing showing the phases of spermatogenesis and their roughly estimated time-intervals in relation to the time of ejaculation. Mitotic proliferation: A and B spermatogonia and preleptotene spermatocytes. Meiosis: primary leptotene spermatocytes through secondary spermatocytes.

Table I. Characteristics of febrile episodes

No. of febrile episodes	No. of men	No. of febrile days
1	10	2–11
2	3	2–7
3	1	1–3
4	1	1–5

Table II. Changes (% and 95% confidence interval) in semen parameters by reported fever prior to semen sampling

	Fever during mitotic proliferation Day -80 to -57 ^a	Fever during meiosis Day -56 to -33 ^a	Fever during spermiogenesis Day -32 to -9 ^a	Fever during sperm maturation Day -8 to 0 ^a
Sperm concentration	5.5 (-21.7; 42.0)	-32.6 (-49.9; -9.2)	-35.0 (-50.5; -14.6)	-0.3 (-38.7; 51.9)
P =	0.726	0.01	0.002	0.877
% normal sperm	-2.8 (-7.5; 2.2)	-4.3 (-9.0; 0.6)	-7.4 (-11.6; -3.0)	-1.4 (-8.7; 6.6)
P =	0.269	0.084	0.001	0.730
% immotile sperm	2.7 (-10.5; 17.9)	-6.4 (-18.7; 7.7)	20.4 (6.0; 36.8)	2.0 (-17.5; 26.1)
P =	0.702	0.355	0.004	0.856

^aOccurrence of fever in relation to day of ejaculation (day of ejaculation = 0).

Table III. Changes (% and 95% CI) in semen parameters per day with reported fever prior to semen sampling

	Fever during mitotic proliferation Day -80 to -57 ^a	Fever during meiosis Day -56 to -33 ^a	Fever during spermiogenesis Day -32 to -9 ^a	Fever during sperm maturation Day -8 to 0 ^a
Sperm concentration	2.3 (-4.1; 9.0)	-7.1 (-12.9; -0.09)	-8.5 (-13.6; -3.0)	-4.8 (-15.4; 7.2)
<i>P</i> =	0.492	0.026	0.003	0.417
% normal sperm	-0.8 (-1.8; 0.3)	-0.2 (-1.3; 0.9)	-1.6 (-2.5; -0.6)	-0.2 (-2.2; 1.8)
<i>P</i> =	0.153	0.714	0.002	0.847
% immotile sperm	0.8 (-2.1; 3.9)	-2.1 (-5.0; 1.0)	4.5 (1.7; 7.3)	-0.9 (-6.2; 4.7)
<i>P</i> =	0.591	0.181	0.001	0.749

^aOccurrence of fever in relation to day of ejaculation (day of ejaculation = 0).

points during spermatogenesis did not seem to significantly affect these sperm parameters. Thus, sperm concentration was affected up to ~56 days after a febrile episode whereas sperm motility and sperm morphology only seemed to be affected up to 32 days after a febrile episode.

There was a large variation in the individual effect of a fever episode on sperm concentration. Eleven of the 15 subjects who experienced fever during the study had a decrease in sperm concentration ranging from -94.2 to -15.2%. Four of the subjects who experienced fever had a non-significant increase (2.7, 5.2, 12.0 and 50.7%). Especially one of the subjects showed a large decrease in sperm concentration (-94.2%) following a fever episode—a fall attributed primarily to a single semen sample. In order to exclude the possibility that this sample significantly influenced the results, all data were reanalysed without this measurement. We found that fever during meiosis caused a significant decrease in sperm concentration (-35.3%; 95%CI: -51.8; -13.2) even when this subject's measurement was excluded and that fever during spermiogenesis still tended to decrease sperm concentration (-14.0%; 95 CI: -36.0; 15.7), but that the effect was no longer significant. Likewise the effect on percentage immotile sperm by fever during spermiogenesis was no longer significant after exclusion of this subject's measurements (12.9; 95% CI -2.3; 30.3); however, fever during spermiogenesis still caused a significant decrease in the percentage of morphologically normal sperm (-6.9%; 95% CI -11.7; -1.8).

Discussion

Our data show that the occurrence of fever has a significant effect on spermatogenesis with certain stages being more susceptible than others. Thus, sperm concentration was significantly affected by fever occurring during the period of meiosis and during the postmeiotic period (spermiogenesis), but not by fever occurring during mitotic proliferation or after completion of spermiogenesis. An effect on sperm morphology and motility could only be seen when fever occurred during spermiogenesis, where the spermatids are undergoing the morphological changes to sperm and acquiring motility. Our data also indicate that sperm parameters were increasingly adversely affected with increasing number of days with fever. The individual response in semen parameters to an incidence of fever, however, showed a large variation with some men even showing an increase in sperm concentration. However, these increases were not statistically significant and presumably

reflect the high intra-individual variation in sperm concentration. It could also be speculated that the individual variation in the effect of fever on semen parameters reflects the severity of the febrile episode. As the men were not requested to measure their body temperature, the reported experienced fever was not in all cases verified by a body temperature measurement, but obviously some of the subjects experienced mild fever for a few days and others had a more severe fever episode. Notably, the one subject showing the strongest deteriorating effect had recorded a 6 day episode of fever with a temperature of ~40°C.

To our knowledge, this is the first prospective longitudinal study in healthy men to evaluate the effect of reported fever on semen quality based on monthly semen samples and daily record of any occurrence of experienced fever. Similar to most clinical cases, we often had no information on the diseases causing the febrile episodes and therefore could not evaluate whether the adverse effects on semen quality were caused by the fever *per se* or by the underlying diseases. However, as different diseases caused the febrile episodes, we find it more likely that the increased body temperature *per se* was the cause.

Few casuistic reports have shown a temporary decreasing effect of a febrile episode on sperm count (MacLeod and Hotchkiss, 1941; MacLeod, 1951; French *et al.*, 1973; Buch and Havlovec, 1991). MacLeod (1951) followed three medical students during a febrile disease of chickenpox and pneumonia and found a marked decrease in sperm concentration and recovery almost 60 days after normalization of the temperature. Motility and morphology, however, recovered faster ~30 days after normalization of the temperature. This time-course is in line with the one obtained in our study. In an earlier study, MacLeod and Hotchkiss (1941) induced artificial fever to 40.5 and 41°C in six donors by electromagnetic induction and found that shortly after the fever treatment the total sperm count fell, reaching the lowest levels at intervals ranging from 25 to 55 days after the treatment. These low levels were maintained for 15–50 days, after which the sperm counts showed a relatively rapid rise. Their study also indicated a significant effect on fever at least during meiosis and probably also the mitotic phase of spermatogenesis. It has been shown in several studies of male contraception that artificial cryptorchidism, which caused an increase in testicular temperature, resulted in a significant reduction in semen quality (Mieusset *et al.*, 1987; Kandeel and Swerdloff, 1988; Mieusset and Bujan, 1994; Wang *et al.*, 1997). Heating of the scrotum for 6–11 weeks by insulation with an athletic support, giving a mean increase in scrotal temperature of 0.8°C, resulted in a severe drop in sperm

count from the third week of treatment with a mean nadir of 14% of the pre-treatment level at the seventh week of treatment. Spermatogenesis recovered in particular from the sixth to the 11th week after treatment was stopped (Robinson and Rock, 1967). Although the time-course of that experiment was not identical with our study, it nevertheless indicated that increased scrotal temperature depresses spermiogenesis, as well as at least part of the meiotic division, followed by a recovery phase. In other experimental human studies, it has been demonstrated that increasing scrotal temperature to 42°C by an electric lamp for 30 min/day for 14–28 days caused an initial increase in total sperm count 1–3 weeks after heating, then a drop to 40–70% of the initial total sperm count 3–11 weeks after heating, followed by recovery of the sperm count from 11 to 13 weeks after heating (Robinson *et al.*, 1968). Taking the timing of the different phases of spermatogenesis into consideration, these results indicate an adverse effect on semen concentration by increased scrotal temperature during mitotic proliferation and meiosis but not during spermiogenesis and epididymal maturation. Fever hardly, if ever, results in an increase in scrotal temperature to 42°C over a prolonged period, which may explain why we, in contrast to Robinson, could not observe any effect of fever during mitotic proliferation. It is possible that only the more severe elevations of body temperature induce an effect also on the mitotic proliferation and number of spermatogonia.

Degenerative changes in rat testes have been found following exposure of the animals to 43°C for 15 min. Chowdhury and Steinberger (1970) found that the pachytene spermatocytes and the early spermatids were the germ cells most sensitive to heat, which is in accordance with our study where the changes due to fever also occurred in the phases of spermatogenesis where pachytene spermatocytes and early spermatids are present. Later studies have also shown that a temperature increase to 43°C for 30 min caused a secondary decrease in rat testicular mass and number of spermatogonia probably due to an effect of spermatogonial renewal or number of stem cells (Setchell *et al.*, 2001). This late effect could correspond to the effect observed in human studies where the temperature was increased to the very high levels (Robinson *et al.*, 1968), which is usually not seen in febrile diseases.

In conclusion, our study showed a significant adverse effect of reported fever on sperm concentration, sperm morphology and motility, and indicates that the phases during spermatogenesis most susceptible to fever with respect to sperm concentration are the meiotic phase and the postmeiotic phase (spermiogenesis) from early primary spermatocytes to early spermatids. Sperm morphology and motility are most susceptible to fever during the postmeiotic phase. Irrespective of the basic mechanism underlying this phenomenon, our findings suggest that history taking prior to sperm banking, semen evaluation and fertility treatments should include accurate information on febrile illnesses during the previous 2 months.

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