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Reduced sperm concentration in a patient from a suspected post-operative infection: a case study

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ABSTRACT

A diagnostic semen analysis should be performed as part of a couple's routine fertility investigations in order to determine sperm quality prior to managing the treatment pathway. The semen analysis report should be considered alongside clinical discussions and a review of both patients' medical history. However, whilst it is part of the standard patient pathway, a regular up-to-date review at each clinical step of a patients' journey is not always performed, which may miss potential clinical changes that could impact the most effective management of the couple. This case study reports the impact on the semen quality of a post-operative infection and hospitalisation of a male patient on a fertility management pathway.

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Introduction

Semen analysis is regarded as a non-invasive determinant of sperm quality for fertility. The current 'gold-standard' method for performing semen analysis is a manual assessment following the World Health Organisations Laboratory Manual for Processing of Human Semen methods [1]. This should be undertaken ideally by a laboratory that has an appropriate level of accreditation to quality standards. Most fertility centres accept a single 'normal' semen analysis without further investigation, unless there has been any significant delay between the initial analysis and the referral for treatment. Normal parameters are generally accepted as those that are equal to or above the lower reference limits as stated in WHO 2010 [1] (see Table 1). In most circumstances, once the possible fertility status of each person is known, a management pathway can be decided.

If assessment of the semen sample demonstrates an abnormality for any parameter, it is advisable to repeat the test three months later [2]. However, if the sample is azoospermic or severely oligozoospermic, a repeat test should be considered more rapidly [3]. Three months is a guideline that allows for a full cycle of spermatogenesis to occur and therefore ensures that any potential abnormality detected is a true representation of the semen quality [4]. It may also demonstrate that there was a false or borderline reading that would require further review. Figure 1 gives a simple overview of a typical fertility pathway, albeit with minimal detail.

Local protocols are used to determine patient management, but in some cases ovulation induction can be initiated using clomifene citrate alongside ultrasound monitoring for a couple whose partner has a semen analysis showing the parameters to be within the normal range [3]. If a repeat semen analysis is performed, continued abnormalities may lead to the request of blood tests to include testosterone, sex-hormone binding globulin (SHBG), follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin. If the sperm concentration is very low, there may also be a requirement to undertake further specialised testing such as karyotyping, Y-chromosome microdeletion testing (for AZF deletions) or cystic fibrosis transmembrane regulator (CFTR) defects. The aim of these tests is to determine if there are endocrine or genetic abnormalities that may aid in the diagnosis and management of the patient.

Case report

A 32-year-old man had a semen analysis performed following a referral by his General Practitioner. Since normal semen parameters were reported [1], there was no obvious male factor infertility. The female patient was therefore prescribed clomifene citrate and the couple were given appropriate patient information and advice for intercourse with ovulation induction.

A follow-up appointment was arranged which was attended by the female partner only. She informed clinical staff that her partner had been treated for 'sepsis' as an in-patient following an operation to correct a pectoral tear. A repeat semen analysis was therefore advised prior to continuing with the ovulation induction to ensure that the potential impact of the acute event had not impacted on the sperm quality.

The results of the second semen analysis demonstrated a 98.1% decrease in sperm concentration (0.5 x 10^6/ml compared to 26.7 x 10^6/ml), total numbers (1.8 x 10^6 sperm/ejaculate compared to 69.4 × 10^6 sperm/ejaculate),

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Table 1. WHO 2010 reference ranges.

Parameter	Lower Reference Limit (5th centiles and their 95% confidence intervals)
Semen volume (ml)	1.5 (1.4–1.7)
Total sperm number ($x10^6$ per ejaculate)	39 (33–46)
Sperm concentration ($x10^6$ per ml)	15 (12–16)
Total motility (progressive motility and non-progressive motility) (%)	40 (38–42)
Progressive motility (%)	32 (31–34)
Sperm morphology (%)	4 (3.0–4.0)
pH	≥7.2
Vitality (live spermatozoa) (%)	58 (55–63)

Table 2. Semen analysis results from patient.

	Date of Semen Analysis		
Parameter	11.04.18	14.03.19	28.05.19
Abstinence (days)	2	4	2
Volume (ml)	2.6	3.6	1.8
pH	8.5	8.0	8.0
Viscosity (normal or high in bead length)	High (>2 cm)	Normal (≤2 cm)	Normal (≤2 cm)
Rapid progressive motility (%)	51	37	75
Sluggish progressive motility (%)	7	19	1
Non-progressive motility (%)	9	11	3
Sperm concentration ($x10^6$/ml)	26.7	0.5*	24.3
Total sperm per ejaculate ($x10^6$)	69.4	1.8*	43.7
Morphology (% normal forms)	5	**	5

*Values below the lower reference limit. **To be not assessed.

with all other parameters remaining within the normal range (see Table 2). Semen analysis concentrations were assessed using the improved Neubauer haemocytometer as shown in Figure 2.

Blood tests were requested in order to determine if there had been any impact on key endocrine function including assessment of thyroid-stimulating hormone (TSH) for thyroid function (see Table 3). His initial test following the second semen analysis showed a reduced testosterone level (4.2 nmol/L) and a marginally reduced SHBG result (12 nmol/L). Repeat testing 46 days later, demonstrated an improvement in both testosterone and SHBG (6.1 nmol/L and 13 nmol/L respectively), although still classed as abnormal, with FSH, LH, prolactin and TSH all within normal parameters. All endocrine tests were performed on Abbott Architect Immunoassay Units using chemiluminescent microparticle methodologies from Abbott Laboratories Abbott Park, Ill, USA). approximately three months after the one preceding the hospital stay, which demonstrated that sperm concentration and total numbers had returned to above the lower threshold reference values. The patient was interviewed by the Clinical Scientist in Andrology and described that he had experienced a decrease in energy levels for some time (period not specified) and that he was still undergoing plastic surgery intervention for the muscle tear.

Hospital records were reviewed for the patient during his hospital admission for potential sepsis. This was authorised by the patient. These demonstrated that post-operatively, the patient was positive for Gram-positive cocci and was given a dose of metronidazole prior to the operation on the muscle tear in late December 2018. In January 2019, the patient attended the accident and emergency department who noted post-operative infection, with an apparent fever and

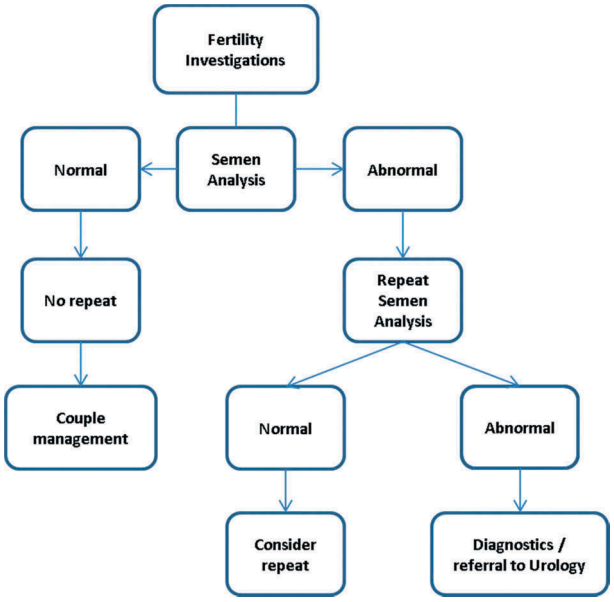

Figure 1. Fertility pathway summary. The flow chart demonstrates a simplistic overview of the pathway. A repeat analysis following an abnormal result may be as soon as possible for severe oligozoospermic patients or after a three-month period. Female patients will undergo simultaneous investigations and the couple managed appropriately. There is no indication that during the 'normal' route, ongoing review of the fertility status is considered in many organisations.

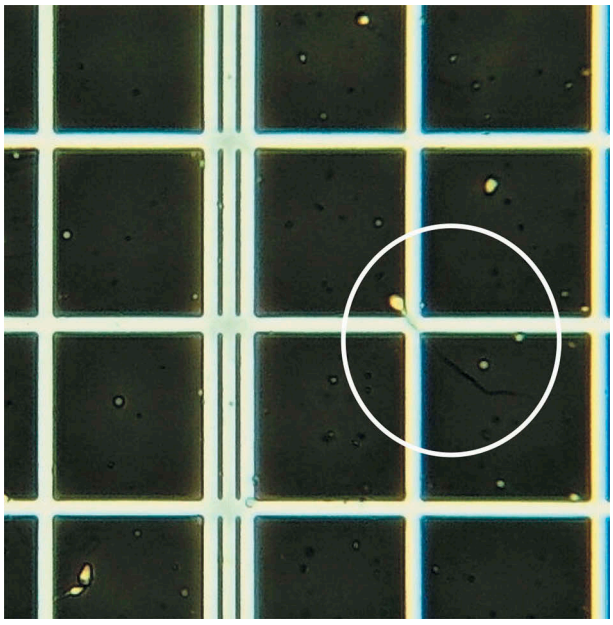

Figure 2. Image demonstrating sperm as observed on the Improved Neubauer Haemocytometer (within the white circle). Each side of the chamber is divided into 9 areas. The central area of the grid is further divided into 25 squares, containing 16 smaller squares held between triple lines. Each of these 25 squares holds 4nl. Concentrations are based on dilutions and areas within the INH counted. The image shown is not a complete chamber.

Table 3. Blood results of the patient following inpatient stay.

	Date of Blood Test	
Test (reference range)	08.04.19	24.05.19
Lutenising hormone (IU/L) (0.6–12.1)	2.4	5.2
FSH (IU/L) (1.0–12.0)	-	4.1
Prolactin (mIU/L) (73–407)	-	241
Testosterone (nmol/L) (8.3–30.2)	4.2*	6.1*
SHBG (nmol/L) (14–71)	12*	13*
TSH (mU/L) (0.4–4.9)	1.6	1.1

*values below the lower reference limit.

discharge from the affected area. The patient was admitted and given flucloxacillin 500 mg and codeine/paracetamol (30/500 mg). The flucloxacillin was administered by intravenous therapy (IV). During the stay the patient was also administered metronidazole (400 mg). The IV antibiotics were given for a period of 23 days but there was no formal diagnosis of septicaemia based on current NICE guidelines [4].

Discussion

The patient was an in-patient for an extended period of time (18 days), due to his pectoral muscle infection. After his initial assessment in accident and emergency, the patient was admitted and treated with flucloxacillin 2 g four times a day and metronidazole 400 mg three times a day. These drugs, when administered at a therapeutic dose, have no known effect on spermatogenesis. However, large doses of metronidazole have shown a negative impact on sperm production in animals [5]. Codeine, an opiate, was also prescribed and administered to the patient. This category of medication has been suggested to affect male fertility in chronic users [6]. The patient was given codeine when he first was admitted for treatment and this continued for the duration of his hospital stay. There is little evidence to suggest that this timeframe would have had an impact on his semen analysis results, particularly as studies do not demonstrate a significant impact on sperm concentration, which was the parameter affected most from review of the results (Table 2).

The influence of stress on health and wellbeing from acute infections should be taken into consideration, particularly as stress can lead to an increase in cortisol and cytokine levels which aid in the inflammatory process [7,8]. Release of glucocorticoids, a class of steroid hormones secreted by the adrenal cortex following activation of the hypothalamus-pituitary axis by inflammatory and stress-related stimuli, is linked to cytokine activity. At physiological concentrations, glucocorticoids are immune modulating and affect all aspects of immune cell function, including shifting the cytokine response pattern to the suppression of inflammation [9]. High levels of glucocorticoids are hypothesised to reduce the effect of testosterone. [10]

Testosterone is essential for spermatogenesis, ensuring that meiosis is completed, and that the spermatid stage is reached [11]. A reduction in testosterone could therefore theoretically restrict the development of the spermatogonia to mature sperm. Monitoring of glucocorticoids would not be part of a patient's routine diagnostic test during hospitalisation and therefore it is impossible to say whether or not there was a significant increase during the acute infection. The endocrine results (Table 3) demonstrated a low testosterone level which could be attributed to the infection and patient's immune responses. Unfortunately, there was no baseline comparison of testosterone and there is minimal data available to determine when spermatogenesis may be significantly impeded due to reductions in testosterone levels [12]. The SHBG levels were minimally reduced, although this would be classed as a borderline abnormal and would be difficult to interpret as significant in the context of the clinical information given.

Another aspect to consider is the body temperature of the patient during this episode (otherwise known as a febrile illness or episode). It has been understood for some time that an increase in temperature can impact negatively sperm quality including motility, concentration and morphology [13]. There is still a wide variation in the clinical definition of what a fever is although it is considered acceptable to take a fever as >37°C with some UK health providers considering it more realistic to define it as any temperature over 37.5°C [14]. The patient's temperature was never >36.8°C during their hospital stay as recorded using a tympanic thermometer. This included when he first presented to accident and emergency before having any treatment for the infection. Patients who do experience fevers are advised that semen analysis results may be affected, and a three-month repeat is advised to ensure that the results are as accurate as possible. As the patient did not have a fever recorded during his stay, it is unclear that this is the reason for the abnormal result although the patient also was on regular co-codamol, which contains paracetamol that has an antipyrexic effect on the body, reducing fever.

It is important to also note that psychological stress is also considered to have an impact on testosterone levels [15]. It is likely that the hospitalisation would have caused a level of psychological stress [16], alongside the physical stress of the infection.

Review of the patient history highlighted that he had previously taken anabolic steroids for recreational activities. This is known to have an effect on testosterone and spermatogenesis by increasing the serum testosterone levels whilst reducing intratesticular concentrations and inhibiting pituitary gonadotrophin secretion (FSH and LH would be extremely low) [17]. However, his first semen analysis was within normal parameters, only after his hospitalisation was there a decrease in his semen quality. The low levels of serum testosterone and previous normal result make it difficult to demonstrate that historic anabolic steroid use was the reason for the abnormal result; therefore, it was most likely related to the acute infection.

There were no known pathologies or external influences other than those discussed that were highlighted during this case study that may have affected the patient's results.

Conclusion

This case report demonstrated that an acute infection and subsequent treatment can have a dramatic deleterious impact on sperm quality. Although sepsis was not diagnosed, there was a clear effect on spermatogenesis, causing a dramatic decrease in the sperm concentration. It is recommended that all patients should have 'real-time' checks of medical history at each step of fertility treatment to ensure that they are managed appropriately. Any acute infections noted should lead to consideration of a repeat semen analysis, three months following recovery and before management plans are finalised.

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