


# Azoospermia: Is it worth waiting for the confirmation of the semen abnormality to start an infertility assessment?

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## Abstract

Azoospermia is found in about 1% of men in the general population and in about 10%–15% of infertile men. Upon discovery of semen analysis abnormality, another test must be performed after an interval of 3 months before any other infertility work-up. This research aimed at evaluating the benefit of waiting for the control test. This retrospective monocentric descriptive study was carried out in the fertility center of the University Hospital of Saint Etienne. All consecutive azoospermic patients diagnosed between January, 2012 and December, 2019 were included. For each patient, two consecutive semen analyses performed 3 months apart were studied. The main focus was on patients whose second semen analysis would have modified the infertility work-up. Amongst the 172 cases under study, the second semen analysis revealed the presence of sperm for three men. Only one of these 3 modified semen analyses was normal. In the observed azoospermic population, sperm was found on the second test in 1.7%. An infertility assessment is necessary after the discovery of azoospermia in the first semen analysis in 99.5%. These results suggest that it is useless to wait three stressful months before starting an infertility assessment for azoospermic population.

## KEYWORDS

azoospermia, infertility, semen analysis

## 1 | INTRODUCTION

Azoospermia is discovered by performing a semen analysis as part of an infertility investigation (Patrick, 1993). It is defined as the absence of spermatozoa after centrifugation of the semen at 3000g for 15 min and thorough examination of the pellet (World Health Organization, Department of Reproductive Health and Research, 2010). It must be distinguished from the absence of semen (anejaculation). Azoospermia is found in about 1% of men in the general population and in about 10%–15% of infertile men (Cocuzza et al., 2013; Jarow et al., 1989; Nieschlag et al., 2010).

Azoospermia may be permanent or transient. Transient azoospermia can be observed after several days of hyperthermia (flu syndrome) or after medication intake (colchicine, salazopyrine, exogenous hormones in therapy or in sports dumping). Hyperthermia and iatrogenic agents lead to hyperoxidation of maturing spermatozoa and to micro disorders of the testis vascularization responsible for destruction of the spermatozoa (Hamdi et al., 2020).

Azoospermia can be classified as obstructive or non-obstructive. The etiological diagnosis of azoospermia is based on various tests performed after detection of a semen analysis abnormality (from mild

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OATS to azoospermia). The theoretical spermatogenesis cycle is 74 days. Therefore, confirmation of azoospermia by another test 3 months later is recommended by the World Health Organization, the American urology Association and the European Urology Association, delaying other investigation (Jarow et al., 2011; World Health Organization, 2010). This recommendation is not based on any high level of evidence and includes all semen analysis abnormalities (azoospermia, and all types of OATS: oligo, astheno and teratozoospermia). In the event of an abnormality on the second spermogram, an infertility assessment should be carried out. Depending on the results, therapies can be considered such as TESE/MESA (surgical biopsy of the testicle and microsurgical aspiration of spermatozoa in the epididymis), allowing the recovery of spermatozoa that can be used in Intra-Cytoplasmic Sperm Injection (ICSI) in 30 to 50% of cases (Corona, 2017).

The absence of etiological research during the 3-month waiting period, is an additional source of stress in the population of infertile couples. The absence of a child in the couple is a source of depression (Galhardo et al., 2016; Madero et al., 2017). Waiting times and lengthy treatment alter the quality of life of the affected couples (Coëffin-Driol & Giami, 2004). Beginning the assessment (hormonal, genetic and imaging investigation) as soon as azoospermia is discovered would improve their care from a psychological point of view and to some extent, in terms of pregnancy rate, by speeding up management.

## 1.1 | Main objective

This study aims at comparing the first semen analysis results with the control test in men diagnosed with azoospermia.

## 2 | MATERIAL AND METHODS

### 2.1 | Study population

A retrospective, descriptive monocentric study of consecutive patients diagnosed with azoospermia was carried out from 1 January 2012 to 31 December 2019 in the Reproductive Medicine Department of the University Hospital of Saint Etienne, France.

Spermograms were performed either in an external specialized laboratory or in the laboratory of the University Hospital. Semen analysis control (control test) was systematically performed in the university hospital laboratory.

Semen samples were collected by masturbation after 2–7 days of sexual abstinence. Their analyses follow the WHO guidelines 5th edition. After complete liquefaction of the ejaculated semen specimen for at least 30 min, ejaculated semen volume was determined by weighing the sample. Azoospermia was defined as the absence of spermatozoa after centrifugation of the semen at 3000g for 15 min and thorough examination of the pellet.

The inclusion criterion was any azoospermic patient discovered by the first semen analysis. The exclusion criteria were severe

oligo-astheno-teratozoospermia (OATS) and/or anejaculation. Risk factors for transient azoospermia were investigated.

The epidemiological characteristics of azoospermic patients (age of patients and partners, Body Mass Index [BMI], smoking, infertility factors of the spouse) were compared with the general population consulting the AMP laboratory of the Saint Etienne University Hospital.

### 2.2 | Ethical aspects

An information notice was distributed to each patient in accordance with European Regulation No. 2016/679 on Data Protection. The study received the approval of the “Terre d’Ethique” committee of the Saint-Etienne University Hospital: IRBN432022/CHUSTE.

### 2.3 | Evaluation criteria

The primary endpoint was the presence of sperm on the second test. The possibility that the initial infertility work-up was unnecessary was also checked.

Infertility testing was performed whenever necessary to define the aetiology of the semen abnormality. This evaluation included a serum total testosterone and Follicle Stimulating Hormone/Luteinising Hormone, a standard karyotype analysis and scrotal ultrasound.

### 2.4 | Statistical test

Statistical analysis was performed using the *Statview*<sup>®</sup> program. Data are expressed as means, standard deviations and percentages/rates. The Chi-square test was used for categorical variables. Continuous variables were tested by Student's *t*-test if normally distributed, or by Mann Whitney's *t*-test if non-normally distributed. A statistical value of  $p < 0.05$  was considered significant.

## 3 | RESULTS

### 3.1 | Study population

During this period, 5465 couples consulted in the Reproductive Medicine Department. The first semen analysis was performed in the laboratory of the Saint Etienne University Hospital for 75.4% of men (4120/5465). The other patients had their test performed in external laboratories.

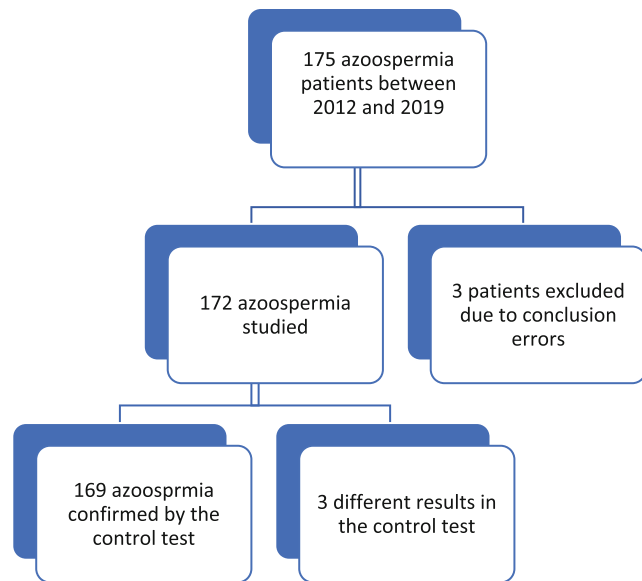
Normospermia was detected in 41% of cases (2241/5465) and an anomaly (OATS to azoospermia) was found in 59% of cases (3224/5465).

In total, 175 azoospermia cases were recorded during this period. The characteristics of the included patients are summarized in Table 1. Out of the 175 azoospermia cases, two were excluded due to

**TABLE 1** Comparison of epidemiological characteristics of the complete azoospermic population versus the general population

	Azoospermic population	General population	<i>p</i>
Workforce	172	5465	
Mean age of patients (standard deviation)	33.5 (±1,4)	34.6	0.025
Mean age of partners (standard deviation)	29.9 (±5)	31.9	<0.001
BMI	25.1	25.5	NS
Active smokers (N)	38.4% (66)	36.4% (1989)	NS
Associated partners pathology (N)	18.6% (32)	21.7% (1186)	NS

Abbreviations: N, population; NS, insignificant.

**FIGURE 1** Flowchart

an erroneous conclusion (very severe OATS) and one case due to an erroneous diagnosis (anejaculation due to psychotropic medication). All 172 remaining patients had primary infertility (Figure 1).

The epidemiological characteristics of the azoospermic population compared to the general population (excluding azoospermia, donation and banking) consulting in the Reproductive Medicine Department are described in Table 1.

### 3.2 | Main objective

Out of the 172 azoosperms, sperm was found on the control test in three cases (1.7%).

One of them (0.5%) was normal, which is the only case where the infertility tests were not needed over a 10-year period. This patient had a risk factor for transient azoospermia, as he presented an influenza-like syndrome with fever (>38.5°C/>101.3 °F) for several days a few weeks before the first semen analysis. The other two cases were cryptozoospermia. (Table 2).

For 99.42% (171/172) of patients, an infertility test was performed. Azoospermia was obstructive in 21.3% (36/169), non-

obstructive in 72.8% (123/169) and the origin was not found in 5.9% (10/169) of cases. The clinical, epidemiological and infertility work-up characteristics of the other two patients whose control test showed sperm are detailed in Table 3.

## 4 | DISCUSSION

The reproductive medicine process is long and difficult for infertile couples. This original study shows that there is very little difference between the first semen analysis and the control test in azoospermic patients. These results suggest that the duration of care of azoospermic patients could be reduced.

The men and their partners were significantly younger than those without azoospermia in the center at stake. Azoospermic patients often have a history that warrants an earlier consultation. This may explain the age difference observed between the two groups. With regard to epidemiological characteristics (smoking, BMI, associated pathology of the spouse), this azoospermic population was comparable to the overall population consulting in the reproductive medicine department.

Regarding the main objective, in 98.3% of cases, the two-semen analyses were identical. The control test found two cryptozoospermia (1.2%) and a normalization of the latter in one case. In the case of severe OATS and azoospermia, the infertility assessment was identical (Jungwirth et al., 2017). Waiting for the confirmation of azoospermia with a control test only avoided 1 infertility assessment out of 172 (0.5%).

In known and described cases of transient azoospermia (Hamdi et al., 2020) (hyperthermia, androgen intake) a normalization of the semen analysis can be observed. This was the case in this population for one patient. This patient had presented an influenza-like syndrome with fever (>38.5°C/>101.3 °F) for several days a few weeks before his semen analysis. Waiting for a theoretical spermatogenesis cycle after the fever had ended should have been done. This would have saved this patient 3 months of stress and anguish/anxiety.

The origin of the azoospermia in this study population (obstructive: AO, non-obstructive: ANO or undetermined: AI) is comparable to what is described in the literature (15%–20% AO; 70% ANO; 10% AI) (Nieschlag et al., 2010; Salonia et al., 2018; World Health Organization, 2010).

**TABLE 2** Main judgement criteria

	Azoospermia	OATS	Normal	Different percentage results	Useless etiological assessment
1st semen analysis (%)	172 (100%)	-	-		
Control test (%)	169 (98.3%)	2 (1.2%)	1 (0.5%)	1.7% (3)	0.5%

**TABLE 3** Patients evaluations

	Patient 1	Patient 2	Patient 3
Age	29	39	32
Intercurrent events before the 1st semen analysis	Flu syndrome with fever >38.5°C	NO	NO
1st semen analysis	Azoospermia	Azoospermia	Azoospermia
Control test	Normal	Cryptozoospermie	Cryptozoospermie
Clinical features and results of the infertility assessment			
Lifestyle	Sedentary	Sedentary	Sedentary
Clinical examination	Normal	Normal	Normal
pH and volume of spermogram	-	pH 8.5 volume 1.2 ml	pH 8 volume 2.5 ml
Hormone balance	-	FSH 9.9 mUI/ml; LH 6.6 mUI/ml; inhibine B 102 g/ml; Testostérone 10.8 nmol/L	FSH 10.2 mUI/ml; LH 5.1 mUI/ml; inhibine B 111 g/ml; Testostérone 11.3 nmol/L
Karyotype	-	46, XY	46, XY
Micro del AZF	-	No	No
Imaging assessment	-	Normal	Normal
Patient outcome			
Origin of the sperm anomaly	-	Undetermined	Undetermined
IVF ICSI with ejaculated sperm collected from the spermogram	-	Failure	1 Birth
TESE	-	Positive	-
IVF ICSI with sperm from TESE	-	1 Birth	-

The use of ejaculated spermatozoa in ICSI allowed one of the two couples in which the man finally had a cryptozoospermia, to achieve pregnancy and to deliver a live-born child. For the second couple, after failure of an ejaculated sperm ICSI, an asynchronous TESE ICSI resulted in pregnancy and live birth. The couple whose control test normalized was lost to follow-up (Table 3).

The main limitation of this study is the small number of patients included. To validate these results and modify the recommendations, it seems interesting to carry out a multicentric study to include a larger number of azoospermic patients. Beginning an assessment immediately is one way of dealing with this distress. Given the average age of the patients (30), every month gained is an additional chance of pregnancy (Biomedicine Agency, 2020). However, it should be emphasized that treatment particularly should be postponed until a confirmatory semen test is performed.

Carrying out a prospective study on the necessity of not waiting for the control test to start an infertility assessment, would make it possible to access the improvement in psychological care and the births rate in reproductive medicine in azoospermic couples.

## 5 | CONCLUSION

In 99.5% (171/172) an infertility assessment is necessary after the discovery of azoospermia on the first semen analysis. These results suggest that it should not wait for the result of the control test to start an infertility assessment. This would reduce the stress caused by the announcement of the diagnosis of azoospermia by proposing active management as soon as the result of the first semen analysis is known. It is however necessary to do the control test in order to search for spermatozoa usable in ICSI and thus avoid unnecessary TESE.

### CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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