FOLIA HISTOCHEMICA ET CYTOBIOLOGICA
Vol. 47, No. 5, 2009
pp. S51-S53

Secretory azoospermia or non-obstructive azoospermia?

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Abstract: In the non-obstructive azoospermia versus the secretory azoospermia it is first necessary to have a clear assessment and definition and then takes care of the patient before the surgical sampling taking into account the age of the woman and *in fine* try to optimize the residual spermatogenesis. Biopsy seems to be the "gold standard" in non-obstructive azoospermia. The mean level of retrieval (extracted) spermatozoa is of 50%, with 20% of pregnancy/cycle and 30% of delivery/couple with a better success for frozen sperm samples.

Key words: human male infertility, non-obtstructive azoospermia, secretory azoospermia, biopsy, spermatozoa, fertilization

Introduction

The word "non-obstructive azoospermia" has been suggested for the first time in 1996 by Devroey to differentiate these patients with those suffering of obstructive azoospermia [3]. In fact that definition is linked to the surgical retrieval of spermatozoa for an ICSI and therefore it is related to the management of the sample in the laboratory. Indeed that term has nothing to do with the histological definition of secretory azoospermia. Thus the levels of sperm extraction are very different as reported recently by Harris in 2008 [7]: 89% of extraction for hypospermatogenesis, 63% for maturation arrest, and 13% for the Sertoli cell only syndrome [9,12].

Results from our experience

Between 1995 and 2007, at the CHRU of Lille, 863 samplings of which 752 from testes (87%) have been performed. The mean age of the patients was 33.1 years (20-59) with a mean second surgery of 1.4%. From this surgery the level of positive extraction was of 64%. In the table 1 when FSH was increased FSH, the level of extraction was of 47% but taking into account only the results from the anatomopathology it is clear that the levels of extraction are different with a record of 58% for abnormal spermatogenesis.

When we have compared the patients with secretory azoospermia, and increased FSH levels, with those with normal FSH but associated with either germ cell aplasia or arrest in germ cell maturation, the levels of sperm retrieval was quite identical. Conversely in patients with hypospermatogenesis the percentage of extraction was 95%. Thus, considering all patients with non-obstructive azoospermia either together or not related to the FSH levels, the amount of extracted sperm could be greatly modified.

Consequently for patients with non-obstructive azoospermia we suggest to take into account the following criteria: increased FSH level and/or germ cell aplasia stop in germ cell maturation, seminiferous tubules atrophy except the patients with congenital absence of vas deferens, ejaculatory dysfunction or excretory azoospermia (Table 2). These considerations are thus important to evaluate the activity of an AMP center, especially it is recommended to clearly define the total number of patients with azoospermia either visited or not by the physician, the method used to classify the patients before sperm retrieval before the analysis of results.

In front of a non-obstrcutive azoospermia a very careful clinical assessment should be therefore realized with special emphasis to previous history i.e age, tobacco, alcohol and obesity are clearly unfavourable factors [2]. The known past history of the patient is significantly in favor of the positive sperm retrieval. However the clinical examination of the patient remains important which can reveal some disorders in the genital tract (hypospadias, varicocele). Conversely the relevance of testicular atrophy is not dramatic for sperm extraction. But a special care should be for the sperm analysis, the way it is performed and mainly to search for a cryptozoospermia present in 15 to 20% of

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Folia Histochem Cytobiol. 2009:47(5): S51 (S51-S53)
10.2478/v10042-009-0063-6

Table 1. Levels of extraction of spermatozoa obtained after surgery in relation with the type of azoopsermia and the histological aspect

	Increased FSH: secretory azoospermia	Increased FSH + APLASIA and arrest with normal FSH: non obstructive azoospermia	Hypo-spermatogenesis with normal FSH azoospermia
Number of patients	427	484	174
Extraction	201 (47%)	223 (46%)	165 (95%)

Table 2. Levels of extraction of spermatozoa by the aetiology of azoospermia

	Number of patients	Number of samples	% extraction
Congenital absence of vas deferens	118 (14%)	129 (14%)	126 (98%)
Obstructive azoospermia	219 (26%)	249 (27%)	222 (89%)
Ejaculatory dysfunction	32 (4%)	34 (4%)	33 (97%)
Non obstructive azoospermia	476 (56%)	494 (55%)	232 (47%)

patients with non-obstructive azoospermia [2]. The increased blood FSH levels is the main criteria of that pathology [5] with a mean value of 10 mIU/ml eventhough some authors suggest to consider lower FSH levels, and inhibin could help also as a predictive parameter for sperm retrieval [2]. In addition a testicular echogarphy should be realized in all these patients with non-obstructive azoospermia since numerous endogenous defects in the testicular tissue have been demonstrated [6]. The last parameters to consider are the caryotype and the genetic evaluation since the frequency of chromosomic disorders is increased in these patients. Nevertheless in the Klinefelter syndrome, the presence of spermatozoa has been demonstrated with a level of sperm extraction of more than 50%; conversely, the Y microdeletions, especially in AZFa and AZFb regions, are a poor pronosotic value for sperm retieval [2,13]. In addition the age of the woman is also very important in the therapeutic strategy.

In 1993, Schoysman *et al.* were the first group to report a positive sperm extraction from testicular tissue to perform ICSI [11]. Nevertheless, from the various meta-analyses available (cochrane data-base) no clear methodology is recommended for sperm extraction [4,7,9,16]. The only parameter to keep in mind is the absence of clear informations concerning the

Table 3. Results obtained after ICSI with spermatozoa collected from surgery

	Normal FSH	Increased FSH	Non obstructive azoospermia	Azoospermia and cryptorchisdism
Couples	295	158	167	95
Cycles	713	324	325	204
Pregnancy/ cycle	161 (23%)	51 (16%)	55 (17%)	39 (19%)
Delivery/ cycle	125 (18%)	39 (12%)	43 (13%)	32 (16%)
Delivery/ couple	147 (50%)	47 (30%)	47 (28%)	39 (41%)

Table 4. Results obtained after ICSI with spermatozoa collected from surgery in relation to the dates of collection. 1995 – 2003: First cycle of samples with fresh sperm, the second with frozen sperm; 2003 – 2007: First and second cycle of samples with frozen sperm

	1995 – 2003	2003 – 2007	1995 – 2003 non obstructive azoospermia	2003 – 2007 non obstructive azoospermia
Couples	268	192	90	77
Cycles	437	288	140	104
Pregnancy/ cycle	87 (20%)	70 (24%)	19 (14%)	24 (23%)
Delivery/ cycle	70 (16%)	55 (19%)	15 (11%)	19 (18%)
Delivery/ couple	83 (31%)	60 (31%)	16 (17%)	19 (25%)

patients studied [13]. Whatever it seemed today that in a patient with a non-obstructive azoospermia a bilateral sampling, "gold standard" should be performed [13] and all discussions nowadays concerned the technical approach either classical testicular biopsy or a microdissection of testis tissue [2].

As a matter of fact, in case of non-obstructive azoospermia, with the extracted sperm used a delivery level/couple of 30% is expected whereas it is of 50% for patient with obstructive azoospermia [10] and its is generally accepted that frozen sperm is more successful than fresh sperm samples [2, 9] which is even more obvious in pateints with non-obstructivre azoospermia.

That approach with frozen samples is in addition very helpful since that avoid (one case of two) to stimulate the woman and to optimize the stimulatory protocol for the FIV/ICSI attempts. In our experience between 1995 and 2006, 1083 attempts ahev been performed with a pregancy rate per cycle of 21%, 16% of delivery/cycle i.e 36% delivery/couple, 42% with cry-

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Table 5. Results obtained after ICSI with spermatozoa collected from surgery in relation with the number of fertilized oocytes (2 PN)

	<5 2PN oocytes	≥5 2PN oocytes	<5 non obstructive azoospermia	≥5 non obstructive azoospermia
Couples	311	125	120	38
Cycles	684	264	218	68
Pregnancy/ cycle	117 (17%)	81 (31%)	29 (13%)	22 (32%)
Delivery/ cycle	88 (13%)	65 (25%)	20 (9%)	20 (30%)
Delivery/ couple	88 (28%)	65 (52%)	20 (17%)	20 (52%)

opreserved-thawed embryo included. More precisely we have recorded some variations between our data taking into account either normal or increased FSH in one hand and, between non-obstructive azoospemia versus cryptorchidism assocaited to non-obstructive azoospemia in an other hand, concerning the level of delivery/couple (Table 3).

For the non-obstructive azoospemia the level of pregnancy/couple was of 18% with frozen sperm whereas it was of 14% with fresh sample. If we compared the data collected in our FIV center (Table 4) we recorded a level of 14% of pregnancy/cycle during the first period (1995-2003) and 23% for the second one (2003-2007) which corresponded to the used of frozen samples in the two cycles. In addition the amount of delivery/couple is higher in the second period (25 vs 8%) compared to the first one (Table 4). The quality of the stimulation for the woman was also important since the level of pregancy/cycle was of 13% when there are less than 5 oocytes fertilized and that level reached 32% when 5 or more oocytes were fertilized (Table 5). The outcome of the pregnancies seemed to be slightly different for the sperm coming from patient with non-obstructive azoospermia compared to ejaculated sperm used in ICSI as suggested by Vernaeve *et al.* [15] who reported an increase of chromosomal and genital disorders.

Acknowledgements: I am pleased to thank Dr S Carreau for the English help.

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