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Are there any predictive factors for successful testicular sperm recovery in azoospermic patients?

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Recovery of testicular spermatozoa from azoospermic patients with testicular failure followed by intracytoplasmic sperm injection (ICSI) is a recent advance in the treatment of male infertility. This study aimed at investigating which parameter(s) may predict succesful testicular sperm recovery. We reviewed 395 testicular sperm recovery procedures and analysed the most frequently available parameters for clinical decision-making in azoospermic patients: (i) presence of at least one single spermatozoon in at least one preliminary semen analysis; (ii) maximum testicular volume; (iii) serum follicle stimulating hormone (FSH); and (iv) presence of spermatozoa in the histology of a randomly-taken testicular biopsy. Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio and accuracy were calculated for the above index parameters in different clinically relevant subgroups using receiver operating characteristic (ROC) curves whenever possible. Spermatozoa were always successfully recovered in patients with normal testicular histological findings (n = 173) or hypospermatogenesis (n = 16) but not in some patients with tubular sclerosis (seven out of 18), Sertoli cell-only pattern (55 out of 112) or maturation arrest (39 out of 76). Histopathology was the best test for predicting successful sperm recovery in the whole population (sensitivity: 86%, specificity: 93%, accuracy: 0.87). In patients with secretory azoospermia, histopathology was again the most accurate parameter (accuracy: 0.74), especially in patients showing Sertoli cell-only pattern (accuracy: 0.83) but not in patients showing maturation arrest (accuracy: 0.55). In patients with serum FSH concentrations >12 IU/l and maximum testicular volume <15 ml, histopathology was not found to be accurate. Semen analysis, maximum testicular volume and serum FSH were not highly predictive in all subgroups studied. Our analysis shows that no strong predictors for successful testicular sperm recovery are available except for testicular histopathology.

Key words: azoospermia/diagnostic study/ROC curves/ spermatozoa/testicular biopsy

Introduction

Recovery of testicular spermatozoa from azoospermic patients for intracytoplasmic sperm injection (ICSI) is a recent advance in the treatment of male infertility. Initially, testicular sperm recovery was performed in patients for whom microsurgical epididymal sperm aspiration (MESA) was not feasible because of extensive scarring or complete absence of the epididymis (Craft *et al.*, 1993; Schoysman *et al.*, 1993). In these case reports, patients were suffering from obstructive azoospermia, i.e. they had normal spermatogenesis. Later, testicular sperm recovery was also performed in azoospermic patients with deficient spermatogenesis or so-called 'non-obstructive azoospermia' (Devroey *et al.*, 1995; Tournaye *et al.*, 1995, 1996). This has led to enthusiastic statements by which there would be 'virtually no forms of male infertility left to cure' (Silber, 1995).

The first births of children conceived with testicular spermatozoa from patients with deficient spermatogenesis leading to secretory azoospermia have been reported recently (Tournaye *et al.*, 1995). Testicular sperm recovery combined with ICSI therefore offers azoospermic men the possibility of fathering their own genetic children even if they do not reveal normal spermatogenesis. As a result many couples who had previously been told that insemination with donor spermatozoa was their only means of conceiving are now willing to explore the possibility of testicular sperm recovery combined with ICSI and enquire about the feasibility of this novel treatment.

While ICSI using testicular spermatozoa is certainly a valid treatment option, testicular sperm recovery may not always be successful in all azoospermic patients. It is therefore very important to determine those factors which may predict a successful recovery procedure. ICSI using testicular spermatozoa from azoospermic patients involves treatment for both partners, i.e. the husband undergoes surgery for testicular sperm recovery and his wife undergoes ovarian stimulation and possibly oocyte retrieval. An unsuccessful sperm recovery procedure, therefore, has important emotional and financial implications. Objective counselling based on predictive factors may offer realistic expectations for both the couple and the physician. This study aims at analysing the predictive value of the most frequently available clinical information as regards sperm recovery in azoospermic patients.

Materials and methods

Patients

In this retrospective observational diagnostic study we analysed a total of 395 testicular sperm recovery procedures performed with azoospermic or virtually azoospermic patients. Testicular sperm

recovery was performed with a view to ICSI or as a diagnostic procedure for the work-up of azoospermia without excluding any azoospermic patient for surgery on the basis of a pessimistic result of one of the index parameters as discussed below. All patients had absolute azoospermia (no spermatozoon found in any of the semen analyses) or virtual azoospermia (history of the presence of at least one spermatozoon in at least one previous semen analysis). In the latter patients, no spermatozoon was found after analysis and centrifugation of at least one semen sample on the day of oocyte recovery.

Testicular sperm recovery

Open excisional testicular biopsies were taken under general anaesthesia or local anaesthesia. The testicular tissue was placed in a Petri dish containing HEPES-buffered modified Earle's medium and transported to the adjacent laboratory. In the laboratory the testicular tissue was teased apart with microscopic glass slides on the warmed stage of a stereo microscope at ×40 magnification. Under an inverted microscope (×400 magnification) the minced tissue was then checked for the presence of spermatozoa. If no spermatozoa were observed, another biopsy specimen was taken. Surgery was stopped when spermatozoa were found or when the whole testicular mass was bilaterally sampled at random. During surgery a randomly taken biopsy was sent for histopathological examination. The findings with regard to testicular histology were classified according to Levin (1979): normal spermatogenesis, germ-cell hypoplasia or hypospermatogenesis, complete or incomplete maturation arrest, complete or incomplete germ-cell aplasia (clinically often referred to as Sertoli cell-only syndrome) and tubular sclerosis.

Statistical analysis

Apart from the overall population, different subgroups were further analysed, i.e. patients with secretory azoospermia and azoospermic patients with hypergonadotrophic hypogonadism [concentrations of follicle stimulating hormone (FSH) > 12 IU/l and testicular volume <15 ml]. Secretory azoospermia was defined according to histopathology. This subgroup included patients not showing normal spermatogenesis or hypospermatogenesis, i.e. patients with complete or incomplete maturation arrest, complete or incomplete germ-cell aplasia and tubular sclerosis. Although a testicular volume <15 ml is indicative of deficient testicular function (Sigman *et al.*, 1991), we chose to define deficient spermatogenesis by histopathology rather than by the clinical diagnosis since in our experience up to 25% of patients where 'non-obstructive' azoospermia was diagnosed according to testicular volume or serum FSH did show normal spermatogenesis as a result of testicular histopathology (Tournaye *et al.*, 1995). Besides, in 15% of patients revealing normal spermatogenesis any site of obstruction remains indeterminate (Matsumiya *et al.*, 1994).

The presence of spermatozoa after wet preparation of the testicular tissue was used as the reference test to assess the potential of different index parameters to predict successful sperm recovery. These parameters were: (i) the documented history of the observation of at least one spermatozoon in at least one semen analysis; (ii) testicular volume of the larger testicle; (iii) serum FSH concentrations measured in IU/l (normal values 1.5–12 IU/l); and (iv) the presence of at least one spermatozoon at testicular histopathological examination of a randomly-taken testicular biopsy. This biopsy was taken before or during surgery for sperm recovery. Whenever histopathology of left and right testicle was discordant, the best histopathological result was considered.

Sensitivity (the probability that an index parameter tests positively when spermatozoa are observed in wet preparation), specificity (the probability that an index parameter tests negatively when spermatozoa were not observed in wet preparation), positive predictive value (the probability that spermatozoa will be found in wet preparation when the index parameter in question tests positively; this value is influenced by the prevalence of spermatozoa in the wet preparations), negative predictive value (the probability that spermatozoa will not be found in wet preparation when the index parameter in question tests negatively; this value is influenced by the prevalence of spermatozoa in the wet preparations), positive likelihood ratio (true positive rate/false positive rate; this value is not influenced by the prevalence of spermatozoa in the wet preparations), and negative likelihood ratio (false negative rate/true negative rate; this value is not influenced by the prevalence of spermatozoa in the wet preparations) were calculated in different clinically relevant subgroups using the Medcalc software (Medcalc, Medcalc Software, Ghent, Belgium). This software package was also used to construct receiver operating characteristic (ROC) curves whenever possible. ROC-curves are plots of all the sensitivity and specificity pairs which are possible for all levels of a particular parameter. They are constructed by plotting the false positive rate defined as:

(number of false positive results) / (number of true negative + number of false positive results)

or 1–specificity on the *x* axis. The *y* axis shows the true positive rate or sensitivity, i.e.

(number of true positive test results) / (number of true positives + number of false negatives).

The best cut-off value discriminating between two conditions, e.g. the presence or absence of testicular spermatozoa, is the value located at the greatest distance from the diagonal. Calculation of the area under the curve provides the quantitative measure of accuracy, i.e. the ability of a particular parameter to discriminate between two conditions. An ROC curve presenting a parameter with no discrimination at all is a 45° diagonal line from the left lower corner (0% true positive rate and 0% false positive rate) to the upper right corner (100% true positive rate and 100% false positive rate) with an area under the curve of 0.5. A parameter with no overlap between the two conditions will discriminate perfectly and has an ROC curve passing along the *y* axis to the upper left corner (100% true positive rate and 0% false positive rate) to end again in the upper right corner with an area under the curve of 1.0 (Zweig and Campbell, 1993).

Results

Testicular sperm recovery

The average age of patients undergoing testicular sperm recovery was 37.5 ± 7.3 (SD) years (range 23–70 years). Overall, in 290 out of 395 patients (73.4%) testicular spermatozoa were successfully recovered. The results according to the different histopathological subgroups are shown in Table I. In 173 procedures (43.8%) the histopathological findings were compatible with excretory duct obstruction as a cause for azoospermia, i.e. histopathology showed normal spermatogenesis.

The median FSH concentration (IU/l) in patients in whom sperm recovery failed was 17.0 ± 1.9 (median ± SE; range 1.5–82.0). This was significantly higher ($P < 0.0001$, Wilcoxon signed rank test) than in patients having a successful testicular sperm recovery (8.2 ± 1.0, range 1.5 ± 75.0). The median volume of the larger testicle (± SE) was significantly higher in the latter patients when compared with that of patients in

Table I. Sperm recovery after wet preparation of excisional testicular biopsies in 395 patients

Histopathological pattern	No.	Prevalence	No. with spermatozoa observed in wet preparation	Recovery rate (%)
Normal	173	43.8	173	100[h]
Germ-cell aplasia[a]	112	28.3	55	50.8[i]
complete	62	55.3[b]	12	19.3[j]
incomplete[c]	50[c]	44.7[b]	43	86.0[k]
Maturation arrest	76	19.2	39	51.3[l]
complete	60	78.9[e]	29	48.3[m]
incomplete[c,d]	16	21.1[e]	10	62.5[n]
Germ-cell hypoplasia[f]	16	4.0	16	100[o]
Tubular sclerosis	18[g]	4.6	7	38.9[p]

[a]Sertoli cell-only pattern.
[b]Percentage of subgroup showing germinal-cell aplasia.
[c]Focal spermatogenesis is present.
[d]Including 15 with observation of spermatocytes or spermatids but no spermatozoa.
[e]Percentage of subgroup showing maturation arrest.
[f]Hypospermatogenesis.
[g]In seven patients spermatozoa were observed in histology.
[h–i]$P < 0.001$ (χ^2 test).
[j–k]$P < 0.001$ (χ^2 test).
[h–l]$P < 0.001$ (χ^2 test).
[h–o]Not significant.
[h–p]$P < 0.001$ (χ^2 test).
[m–n]Not significant.

Table II. Sperm recovery rate after wet preparation of excisional testicular biopsies according to different parameters[a]

Parameter analysed	All azoospermia	Secretory azoospermia[b]	Hypergonadotrophic hypogonadal azoospermia[c]
Serum FSH (IU/l)			
<12	83.3[d]	45.0	–
12–24	58.3[e]	52.0	61.5
>24	48.0[f]	38.1	46.7
Testicular volume (ml)			
⩾15	83.6[g]	68.7	–
6–14	51.7[h]	48.1	50.0
⩽5	54.8[i]	51.7	57.1
Semen analysis			
⩾1 spermatozoon	76.0	62.3[l]	58.3
no spermatozoon	72.9	44.1[m]	50.0
Histology			
⩾1 spermatozoon	95.4[j]	82.3[n]	77.8
no spermatozoon	31.3[k]	31.3[o]	42.1

See Table III for numbers of samples tested.
[a]Differences not significant unless marked otherwise.
[b]Testicular histopathology not showing normal spermatogenesis or hypospermatogenesis.
[c]Testicular volume <15 ml and serum follicle stimulating hormone (FSH) concentration > 12 IU/l.
[d–e]$P < 0.001$ (χ^2 test).
[d–f]$P < 0.0001$ (χ^2 test).
[g–h]$P < 0.01$ (χ^2 test).
[g–i]$P < 0.01$ (χ^2 test).
[j–k]$P < 0.0001$ (χ^2 test).
[l–m]$P < 0.02$ (χ^2 test).
[n–o]$P < 0.0001$ (χ^2 test).

whom recovery failed: 17.5 ± 1.0 (range 2.0–30.0) versus 7.0 ± 1.2 (2.0–26.0) ($P < 0.0001$, Wilcoxon signed rank test).

Table II summarizes the outcome of testicular wet preparations according to the different clinical subgroups. As can be seen, neither high FSH, nor small testicular volume precluded successful testicular sperm recovery in the groups analysed.

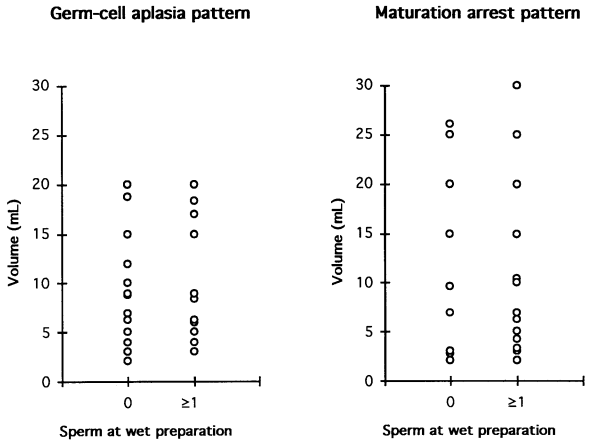

Figure 1. Distribution of the maximum testicular volume in patients with and without successful testicular sperm recovery in the patient subgroups showing germ-cell aplasia and maturation arrest.

Figures 1 and 2 show the distribution of the maximum testicular volume and serum FSH in patients with and without successful testicular sperm recovery in the subgroups showing germ-cell aplasia and maturation arrest.

Prediction of successful testicular sperm recovery

Diagnostic accuracy, sensitivity and specificity, predictive values and likelihood ratios were analysed for semen analysis, serum FSH, testicular volume and testicular histopathology according to the availability of this information in different clinically relevant subgroups.

All azoospermic patients

As shown in Table III, the presence of at least one spermatozoon in at least one semen analysis report was not found to be an accurate parameter predicting successful testicular sperm

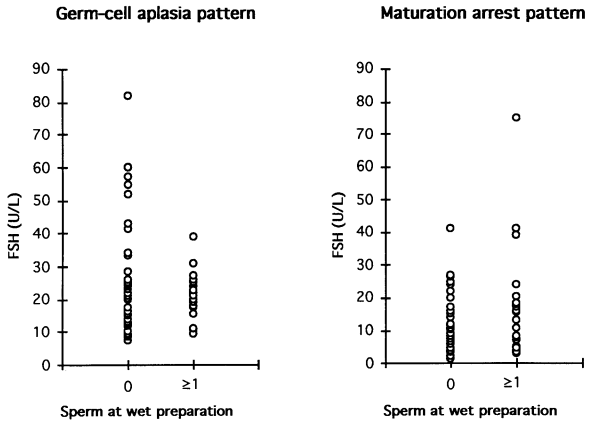

Figure 2. Distribution of the serum follicle stimulating hormone (FSH) concentrations in patients with and without successful testicular sperm recovery in the patient subgroups showing germ-cell aplasia and maturation arrest.

recovery for the overall population. This parameter had a low sensitivity and specificity. Best testicular volume or serum FSH concentration too were not found to be accurate, both showing low sensitivities. Figure 3 shows the ROC curves for these parameters, together with those of other subgroups as decribed below. The histopathological findings in a randomly taken testicular biopsy were found to be very accurate with a high sensitivity and specificity, 85.8 and 92.9% respectively.

Patients with secretory azoospermia

In the group of patients with secretory azoospermia, i.e. with a histology not revealing normal spermatogenesis or hypospermatogenesis, semen analysis, testicular volume and FSH concentration were not found to be accurate parameters for predicting successful sperm recovery. At the best cut-off value of 21.9 IU/l, FSH showed the highest sensitivity (71.7%) but a specificity of only 41.7%. The odds in favour of successful sperm recovery when FSH was ⩽21.9 IU/l were ~1–1 while an FSH >21.9 IU/l gave odds in favour of sperm recovery failure of 1.8 to 1. The odds in favour of a successful sperm recovery given a testicular volume of at least 6.3 ml were ~1–1 and the odds in favour of not finding spermatozoa at wet preparation were again ~1–1 when the volume was <6.3 ml. For semen analysis, the odds in favour of a of successful sperm recovery were 1.7 to 1 given a positive test. When no spermatozoa were reported at semen analysis the odds in favour of sperm recovery failure were 1.3 to 1. In this subgroup, histopathology was again found to be the best parameter with an accuracy of 0.74 but a sensitivity of only 58.8% and a specificity of 88.5%. The odds in favour of successful sperm recovery when histopathology revealed at least one spermatozoon were 5.1 to 1 while the odds in favour of sperm recovery failure were 2.2 to 1 when no spermatozoon was observed.

Considering only patients with hypogonadism, i.e. whose larger testicular volume was <15 ml, indicative for testicular failure, histopathology was again found to be the best parameter in predicting successful sperm recovery (accuracy: 0.73, sensitivity: 63.6% and specificity: 85.2%). Surprisingly, FSH concentration was not accurate (0.54) with both low sensitivity (65%) and specificity (50%) at the best cut-off value of 20.3 IU/l. Information on semen analysis too presented a low accuracy (0.47) with poor sensitivity (27.2%) and specificity (71.4%). In a subgroup of patients with elevated FSH, i.e. serum FSH >12 IU/l, the same held true. Semen analysis and testicular volume measurement were not accurate parameters (accuracy of respectively 0.56 and 0.43) while histopathology did much better (accuracy of 0.76), with a sensitivity of 69.1% and a specificity of 83.7%.

Hypergonadotrophic hypogonadal azoospermic patients

In patients showing the classic triad indicative of deficient spermatogenesis, i.e. azoospermia, elevated FSH (>12 IU/l)

Table III. Prediction of successful testicular sperm recovery by different clinical parameters

Group analysed	Parameter	*n*	Accuracy	Sensitivity	Specificity	PV+[a]	PV–[b]	LR+[c]	LR–[d]	Cut-off value
All azoospermia										
	semen analysis	395	0.42	28.1	79.2	76.0	72.9	1.3	0.9	1
	testicular volume	122	0.69	60.7	73.7	83.6	45.9	2.3	0.5	12[e]
	serum FSH	233	0.69	53.8	80.8	86.0	44.4	2.8	0.6	8.7[f]
	histopathology	395	0.87	85.8	92.9	95.4	68.7	12.1	0.1	1
Secretory azoospermia[g]										
	semen analysis	206	0.58	38.2	77.9	62.9	56.3	1.7	0.8	1
	testicular volume	78	0.51	56.1	54.1	57.5	52.6	1.2	0.8	6.3[e]
	serum FSH	132	0.50	71.7	41.7	50.6	63.8	1.2	0.7	21.9[f]
	histopathology	206	0.74	58.8	88.5	83.3	68.7	5.1	0.4	1
Hypergonadotrophic hypogonadal azoospermia[h]										
	semen analysis	31	0.52	66.7	37.5	58.3	50.0	1.1	0.9	1
	testicular volume	31	0.60	73.3	56.2	61.1	69.2	1.7	0.5	6.3[e]
	serum FSH	31	0.54	66.7	50.0	55.6	61.5	1.3	0.7	20.3[f]
	histopathology	31	0.61	40.0	81.2	75.0	57.9	2.1	0.7	1

[a]Positive predictive value (PV).
[b]Negative predictive value.
[c]Positive likelihood ratio (sensitivity/1–specificity) (LR).
[d]Negative likelihood ratio (1–sensitivity/specificity).
[e]Best criterion value according to receiver operating characteristics (ROC) analysis, expressed in ml.
[f]Best criterion value according to receiver operating characteristics (ROC) analysis, expressed in IU/l.
[g]Testicular histopathology not showing normal spermatogenesis or hypospermatogenesis.
[h]Testicular volume <15 ml and serum follicle stimulating hormone (FSH) > 12 IU/l.

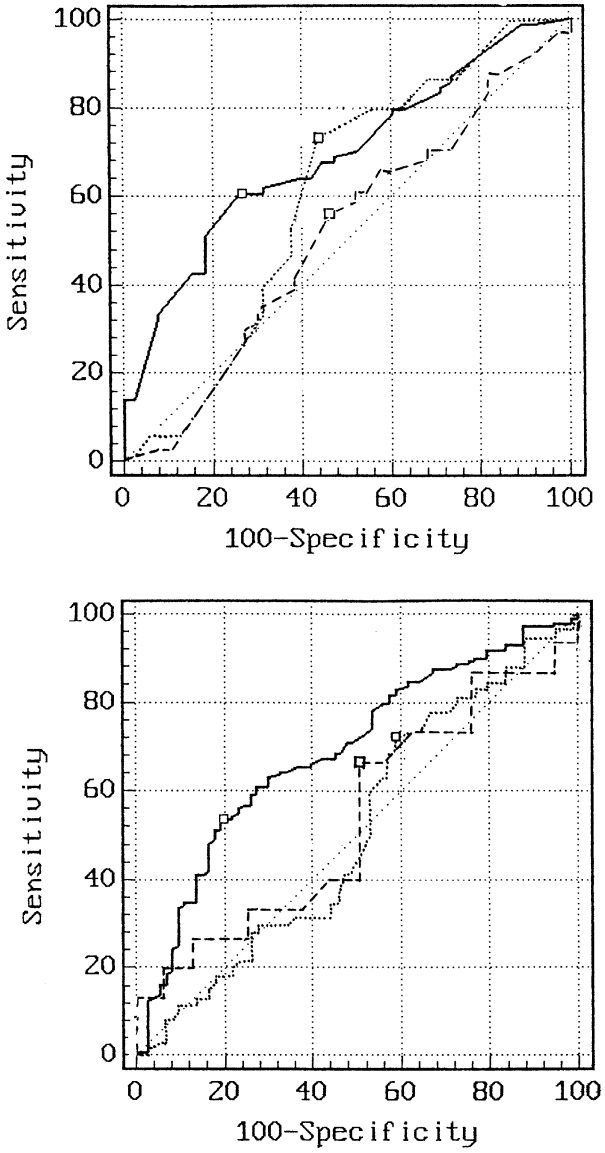

Figure 3. Receiver operating characteristic (ROC) curves of the maximum testicular volume (upper graph) and serum follicle stimulating hormone (FSH) concentrations (lower graph) for all azoospermic patients (solid line), for patients with secretory azoospermia (dotted line) and for azoospermic patients with hypergonadotrophic hypogonadism (dashed line).

and hypogonadism (testicular volume <15 ml), testicular spermatozoa were successfully recovered in 15 out of 31 cases (48.4%). Here both testicular volume and histology proved to be the most predictive parameters, yet with low accuracies of 0.60 and 0.61 respectively. Testicular volume had the highest sensitivity but a low specificity while histology had a low sensitivity but a high specificity (see Table III).

Azoospermic patients with germ-cell aplasia and maturation arrest

Since the majority of patients with secretory azoospermia or hypergonadotrophic hypogonadal azoospermia revealed germ-cell aplasia (n = 112) or maturation arrest (n = 76), we also analysed these two subgroups separately. Figures 1 and 2 show the overall sperm recovery according to testicular volume and serum FSH for patients with maturation arrest and germ-cell aplasia at testicular histopathology.

As can be seen from Table IV, histopathology was a strong predictor in patients with germ-cell aplasia (accuracy 0.83) but, in contrast, it was found a very weak predictor in patients with maturation arrest (accuracy 0.55). Again, all other index parameters were found to be weak predictors in both groups.

Discussion

The overall sperm recovery rate over 395 testicular biopsy procedures with wet preparation was 73% in this series. In patients with deficient spermatogenesis as a cause of absolute or virtual azoospermia this figure fell to 50%. Yet in a subgroup of azoospermic men with hypergonadotrophic hypogonadism the recovery rate was still 48.4%.

Our analysis was aimed at validating the usefulness of the most frequently available parameters for clinical decision making, i.e. semen analysis, testicular volume measurement, serum FSH concentration and histopathological examination of a randomly taken biopsy. Since this is a retrospective analysis, not all parameters were available for all patients. However, all azoospermic patients were accepted for surgery whatever the results of the above parameters. In this way work-up bias was excluded. We chose to validate these parameters using ROC curve analysis whenever possible. In ROC curve analysis many efficiencies of all decision levels can be calculated, resulting in an overall quantification of accuracy which is not affected by the prevalence of a condition, e.g. the presence or absence of spermatozoa in a wet preparation (Zweig and Campbell, 1993). But ROC curve analysis also provides a qualitative measure since, for each index parameter, it provides the best cut-off value with the highest clinical usefulness.

Generally, histology was found to be the most accurate parameter. The observation of at least one spermatozoon during histopathological examination of testicular tissue had a positive likelihood ratio of 12.1 and a negative likelihood ratio of 0.15. Since a good discriminative test should have a positive likelihood ratio of at least 5.0 and a negative likelihood ratio of 0.2 or less, histopathology is definitely a good predictor for successful sperm recovery for the overall azoospermic population.

However, histopathology was inaccurate in patients with secretory azoospermia as defined by histopathology or as defined by all typical clinical signs, i.e. azoospermia, hypogonadism and elevated FSH concentration. This can be explained by the fact that in patients with normal spermatogenesis or hypospermatogenesis, spermatozoa will invariably be observed in a single testicular specimen taken at random and spermatozoa will always be recovered in wet preparation. These patients made up 47.8% of the overall population studied. In the other patients, a single biopsy taken at random may not reveal spermatozoa while multiple samples taken for wet preparation still may reveal spermatozoa (Tournaye *et al.*, 1995). If multiple biopsies were sent for histopathology too, the accuracy in the population suffering from secretory azoospermia would probably again be much higher. In these

Table IV. Prediction of successful testicular sperm recovery in patients with maturation arrest and germ-cell aplasia patterns in testicular histopathology

Group analysed	Parameter	*n*	Accuracy	Sensitivity	Specificity	PV+[a]	PV–[b]	LR+[c]	LR–[d]	Cut-off value
Germ-cell aplasia[e]										
	semen analysis	112	0.59	34.5	82.4	65.5	56.6	2.0	0.8	1
	testicular volume	39	0.59	45.0	73.3	4.3	56.0	1.7	0.7	6[f]
	serum FSH	60	0.56	69.6	51.4	47.1	73.1	1.4	0.6	22.8[g]
	histopathology	112	0.83	78.2	87.7	86.0	80.6	6.4	0.2	1
Maturation arrest										
	semen analysis	76	0.62	43.6	81.1	70.8	57.7	2.3	0.7	1
	testicular volume	30	0.56	47.4	72.7	75.0	44.4	1.7	0.7	6.3[f]
	serum FSH	57	0.55	44.8	71.4	61.9	55.6	1.6	0.8	15.8[g]
	histopathology	76	0.55	25.6	86.5	66.6	52.5	1.9	0.9	1

[a]Positive predictive value (PV).
[b]Negative predictive value.
[c]Positive likelihood ratio (sensitivity/1–specificity) (LR).
[d]Negative likelihood ratio (1–sensitivity/specificity).
[e]Sertoli cell-only pattern.
[f]Best criterion value according to receiver operating characteristics (ROC) analysis, expressed in ml.
[g]Best criterion value according to receiver operating characteristics (ROC) analysis, expressed in IU/l.
FSH = follicle stimulating hormone.

subpopulations a single-sample biopsy for histopathology has too high a false negative rate for this test to be accepted as a useful predictor. If no spermatozoa were observed in a random single-sample biopsy, multiple biopsies taken for wet preparation revealed spermatozoa in 41% of the secretory azoospermic group and in 53.3% of the hypergonadotrophic hypogonadal azoospermic group.

On the other hand, when the main histopathological patterns of these subgroups, i.e. germ-cell aplasia and maturation arrest, were analysed separately, histopathological examination was found to be an accurate predictor in patients with germ-cell aplasia but not in patients with maturation arrest. Thus obviously the observation of focal spermatogenesis during histopathology is much more difficult in patients with maturation arrest than in patients with germ-cell aplasia. Because of the differences in accuracy it is therefore preferable to predict probabilities according to the specific histopathological diagnosis, i.e. germ-cell aplasia or maturation arrest, rather than according to the subgroup of secretory azoospermia.

All other clinical parameters studied turned out to be poor predictors of successful testicular sperm recovery in all groups analysed. The findings from semen analysis turned out to be the weakest predictor for all groups studied. We have taken the presence or the report of at least one spermatozoon in at least one semen analysis as a parameter. This parameter, however, may have been more accurate if multiple semen analyses including centrifugation had been performed prospectively. Furthermore, about half of the population studied had normal spermatogenesis. This high incidence of excretory duct obstruction causing absolute azoospermia may therefore attenuate the predictive power of this parameter in the overall population.

The concentration of FSH was also found to be a poor predictor in all groups studied. It is generally assumed that most patients showing a Sertoli cell-only pattern in their testicular histopathology have elevated FSH concentrations, while most patients with a maturation-arrest pattern revealed by histology are assumed to have normal FSH concentrations (Martin-du-Pan and Bischof, 1995). As shown in Figure 2, however, there is an important overlap in the distribution of normal and elevated FSH concentrations in these two major subgroups of the secretory azoospermic population, irrespective of the presence or absence of spermatozoa in the wet preparation. This overlap in distribution probably explains the low accuracy of this parameter in predicting successful testicular sperm recovery.

The same is probably true for the volume measurement of the larger testicle. Patients showing Sertoli cell-only pattern in histopathology are assumed to have small and soft testicles, while testicles of patients showing maturation arrest pattern at histopathology are assumed to have a normal testicular volume. But again, as can be seen from Figure 1, for testicular volume too there is a wide distribution of the testicular volume with an important overlap between the populations with and without spermatozoa observed at wet preparation. Thus a large testicular volume or a normal serum FSH does not indicate successful testicular sperm recovery in patients with a Sertoli cell-only pattern in their testicular histopathology. Conversely, in patients showing a maturation arrest pattern in their testicular histopathology, a low testicular volume or a high FSH does not preclude successful testicular sperm recovery.

Although our analysis does not indicate strong predictors for successful testicular sperm recovery except for histopathology, some guidelines for patient counselling may, nevertheless, be proposed.

If a couple suspected of suffering from infertility because of secretory azoospermia considers failure of testicular sperm recovery as a serious psychological and/or financial burden, then counselling should be based on tests with a low false positive rate, thus a high specificity. A positive histopathology of a preliminary single-specimen testicular biopsy will correctly predict successful testicular sperm recovery in 83.3% of cases. However, a negative result will predict recovery failure in only 68.7% of cases. If the couple rejects a preliminary testicular biopsy, then the result of a standard semen analysis may serve as a guide, since this test showed the second-highest

specificity (77.9%) in this subgroup. Yet the predictive value of a positive test was only 62.9% with the odds in favour of recovering spermatozoa after a positive test of only 1.7 to 1.

If another patient does not accept the idea of using donor spermatozoa as an alternative and considers testicular sperm recovery as the only means by which to father children, then tests should be chosen with a high sensitivity regardless of the specificity. Here again, the result of a preliminary testicular biopsy will be the best predictor. However, considering the high false negative rate of 42%, such a patient will usually prefer to undergo a testicular sperm recovery procedure in any case.

If the biopsy, however, shows a germ-cell aplasia pattern (Sertoli cell-only), the probability that spermatozoa will be recovered is 86% when focal spermatogenesis is observed. The probability that no spermatozoa will be recovered is 80% when no focal spermatogenesis is observed. If the patient has maturation arrest, the situation is less clear, the figures being only 66.6 and 52.5% respectively.

Our analysis shows clearly that no strong predictors for successful testicular sperm recovery are available except for testicular histopathology. Considering the important psychological and financial implications of a treatment by ICSI with testicular spermatozoa, a preliminary single-specimen testicular biopsy may be preferable in each patient suspected of suffering from secretory azoospermia. Although the accuracy of this parameter is limited in this subgroup, a strong prediction may be made if the testicular biopsy shows a germ-cell aplasia pattern.

Overall, a preliminary multiple-specimen testicular biopsy with a diagnostic wet preparation of the testicular tissue may be more efficient in predicting a successful testicular sperm-recovery procedure. However, more prospective research should be done to prove this and to show that this approach does not hinder later treatment of hypogonadic patients through intracytoplasmic testicular sperm injection. Reduction of the testicular mass with removal of those parts with active spermatogenesis or impairment of testicular function because of post-sampling fibrosis or auto-immune response may compromise the future outcome.

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