



Andrology

Sperm Retrieval Rates in Subgroups of Primary Azoospermic Males

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Abstract

Objectives: Men presenting with primary infertility and azoospermia may be offered surgical sperm retrieval (SSR) as a prelude to intracytoplasmic sperm injection (ICSI). We evaluated sperm retrieval rates in subgroups of men with azoospermia, based on obstructive aetiology, testicular volume and FSH.

Methods: 106 patients with primary infertility underwent clinical evaluation and SSR with percutaneous epididymal aspiration (PESA) and/or testicular sperm extraction (TeSE) by a single urologist over a five year period. Ten percent of this group (11 patients) had a clear cause of obstruction, congenital absence of the vas deferens (CBAVD), labelled group A. Ninety percent (95 patients) had no definite cause of obstruction, labelled group B.

Results: All eleven patients in group A had adequate sperm retrieved, compared with 56% of 95 men in group B. Clinical pregnancy and live birth rates were 47% and 44% for group A respectively compared with 21% and 20% for group B. Twenty-one men had testes <4 cm and FSH > 10; a significantly lower sperm retrieval rate was seen in this subgroup (29%) compared to men with normal testicular volume and FSH (77%), $p = 0.0001$, which corresponded to a LBR of 28% and 14% respectively.

Conclusions: In the absence of testicular histology prior to SSR clinical parameters can be used to aid in counselling. Azoospermic males with normal sized testes and normal FSH can expect acceptable numbers of sperm to be retrieved by SSR for ICSI. Less than one third of men with raised FSH and small testes will have successful SSR.

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1. Introduction

Intra-cytoplasmic sperm injection (ICSI) has made vast differences to the prospects of live birth rates in male patients presenting with primary infertility. The first report of a live birth following ICSI was in 1995 [1] and both ejaculated sperm and sperm recovered using surgical sperm retrieval (SSR) have been used successfully in this process. SSR can be carried out using percutaneous aspiration of the epididymis (PESA) or testis (TeSA), or by testicular extraction (TeSE), which can be open, closed, or with microdissection. Successful outcome of ICSI measured by live birth rates has been shown to be independent of the type of procedure [2]. There are still conflicting reports as to which procedure is superior, with most studies recommending PESA and open TeSE [3–5]. SSR is generally tolerated well and the complication rate is low from both PESA and TeSE [6].

Sperm recovery in azoospermic males depends on the testicular histology [7]. Therefore, testicular biopsy has been used to predict successful SSR [8]. However, biopsy is an invasive procedure, which may cause damage to the testis, and the cost implication of biopsy is similar to that of negative TeSE. Previously, the terms obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) have been applied in azoospermia, OA being associated with normal spermatogenesis, and NOA with different degrees of impaired spermatogenesis. It has been demonstrated that retrieval rates in NOA are significantly lower than in OA [9]. However, these terms can be confusing and inaccurate, as the presumed diagnosis is now often made without histology, and on the presence or absence of clinical features associated with obstruction. An obstructive cause is sometimes clear, such as in congenital bilateral absence of the vas deferens (CBAVD), or following a previous vasectomy. Sperm retrieval rates in OA have, not surprisingly, been quoted around 100% [10]. However there are no studies showing a clear relationship between clinical parameters associated with obstruction, such as previous infection or surgery and normal testicular histology, and up to 15% of men have obstruction at the level of the rete testis [11]. There may be normal spermatogenesis in this group of OA males, with no clinical findings to suggest obstruction.

Research has been directed into finding other parameters that may predict successful SSR. Maturation arrest, a cause of NOA, can be suspected clinically with a high serum FSH [12] and small testes, but again, only accurately

diagnosed with biopsy [13], and although hypergonadotrophic hypogonadism is associated with poorer outcomes of SSR, no study has been able to show these factors to be predictive [8,12]. Inhibin is another parameter that has been shown to be associated with maturation arrest, but this is not used routinely, and although it correlates with impaired spermatogenesis more closely than FSH, it is not diagnostic [14].

Doppler ultrasonography has recently been used to correlate testicular blood flow with successful sperm recovery in azoospermic males [15]. A positive PESA prior to TeSE has been shown to be a good predictor of successful sperm recovery from TeSE [16]. However, this is an invasive procedure and if patients want to go ahead with sperm retrieval, then PESA followed by TeSE, if necessary, can be performed at the same time. Therefore, no non-invasive clinical criteria have been shown to accurately predict the outcome of sperm retrieval in azoospermia.

The primary aim of this study was to determine the rates of successful sperm retrieval (PESA and TeSE), clinical pregnancy rates and live birth rates in subgroups of men with primary infertility; those with an obvious obstructive cause, group A, and those with no definite obstructive cause, group B. We also aimed to perform further analysis on those with normal testes and FSH and those with abnormalities in these parameters, so that azoospermic males presenting for treatment can be informed of success rates of SSR based on clinical features alone.

2. Patients and methods

A retrospective analysis of 143 cases of primary azoospermia presenting between 2000 and 2004 was undertaken. These cases presented to a single consultant urological surgeon as part of a joint fertility clinic with a single senior clinical embryologist. All males were diagnosed using at least two samples for semen analysis. The partners of the azoospermic males had been investigated or were being investigated appropriately. Clinical parameters including age, history of infertility, previous infection, or relevant surgical procedures were recorded. Patients were assessed with clinical examination, measurement of testicular size, and a subjective assessment as to whether epididymal distension was present. Serum FSH was performed on all patients, cystic fibrosis gene testing was carried out for those with CBAVD, and karyotype was performed in males with any feature to suggest an abnormality. Patients were divided into 2 groups based on clinical grounds alone. Those in group A, had a clear cause of obstruction, namely CBAVD. Those in group B had no definite cause of obstruction. Those patients who had features that are associated, but not diagnostic of obstruction, such as infection or epididymal distension were considered as part of group B

due to the lack of evidence that these features correlate with obstruction. Therefore group B consisted of a mixture of OA and NOA.

PESA and TeSE (open and closed) were offered to all patients so that if the PESA retrieval proved to be poor, TeSE could be performed at the same time. PESA was performed under general anaesthetic with a 25 gauge needle and syringe containing 0.5 ml sperm preparation medium (MediCult a/s, Møllehaven 12, 4040 Jyllinge, Denmark). The needle was inserted into the head of the epididymis, with up to four passes per side and the aspirate was passed through the needle into a sterile plastic tube and examined for spermatozoa immediately by the clinical embryologist. If sufficient sperm were seen, straws were cryopreserved in SpermFreeze™ medium (Fertipro NV, Industriepark Noord 32, 8730 Beernem, Belgium).

Open TeSE was carried out either following a poor or negative PESA, during the same anaesthetic, or in preference to PESA. This was performed through a transverse scrototomy. Four 3 mm biopsies were taken in a spiral manner around the testis, the orchiotomies closed with 5/0 PDS, and a layered closure performed with 3/0 monocryl. Again, sufficient sperm was cryopreserved and the embryologist analysed pre and post thaw motility and morphology, and judged suitability for ICSI.

2.1. ICSI method

Ovarian stimulation was achieved using either a long or short protocol (co-flare or boost) depending on the patient's age and basal serum levels of follicle stimulating hormone (FSH) or previous cycle history. Oocytes were collected 36 hours after hCG injection. Cumulus cell removal was achieved by placing the oocytes briefly in Hyaluronidase medium (Medi-Cult), the remaining cells were removed with a fine bore pipette. Only oocytes which had extruded a polar body were selected for ICSI (metaphase II). Microinjection was carried out on an Olympus inverted microscope with Hoffman modulation optics. A single morphologically normal motile sperm was selected, immobilised and the aspirated into the injection needle. Each oocyte was firmly attached to the holding pipette with the polar body at 6 o'clock. The injection needle entered the oocytes at 3 o'clock and breakage of the oolemma was achieved by gentle aspiration followed by careful deposition of the sperm into the cytoplasm. After injection the oocytes were washed in Universal IVF medium (Medi-Cult) and cultured together overnight in a 200 µl drop Universal IVF medium under liquid paraffin.

2.2. Embryo culture and selection

17–18 hours post insemination the oocytes were observed for pronuclear formation. The criterion for normal fertilisation was the presence of two pronuclei. Four embryos were selected for continued culture and the remaining embryos were cryopreserved. On day 2 after egg recovery, a maximum of two embryos were selected for transfer using morphological criteria. Pregnancy following embryo transfer was detected by serum hCG 15 days post implantation and confirmed by the presence of a fetal heart at 5 weeks.

Statistical analysis was performed with unpaired t tests and Fisher's exact test.

3. Results

143 patients (median age 34; range 22–55) attended with primary azoospermia. Of these 12 patients (8%) had CBAVD, labelled group A and the remaining 131 patients (85%) were constituted group B. 106 out of 143 (74%) proceeded to SSR, 11 of group A and 95 of group B. The median age of the 106 males that proceeded to SSR was 34, compared to an age of 36 for the 37 males who did not proceed.

Overall, 64 patients had adequate sperm retrieved for ICSI. PESA was performed on 54 patients, and 24 were positive (see Table 1). TeSE was performed on 82 patients, and 40 were positive. All eleven (100%) of the CBAVD patients had adequate sperm retrieved for ICSI, 7 from PESA and 4 from TeSE. This compared with 53 positive retrievals out of 95 (56%) in group B, 17 from PESA, and 36 from TeSE (see Table 1). Eight out of 11 patients with CBAVD were carriers of the cystic fibrosis gene, and 7 of these patients had positive PESAs. All patients who had a karyotype tested were normal (46XY).

Testicular size ranged from 1 cm to 8 cm, median 5 cm, and FSH ranged from 1 IU to 50 IU, median 7 IU. A bar chart of FSH ranges and successful sperm retrieved is shown in Fig. 1a. The median FSH for patients with positive sperm retrieval was 7 IU, compared with that for negative retrieval, 12.8 IU. 53

Table 1 – Sperm retrieval rates and live birth rates in primary infertility in males with CBAVD (group A) and no definite cause of obstruction (group B). A twin birth was counted as one live birth event

Clinical Diagnosis	Number patients	+ve PESA	+ve TeSE	Successful sperm retrieved	Number progress to ICSI	ICSI treatment Cycles	Clinical pregnancies (CPR)	Live birth events (LBR)
Group A	11	7 (64%)	4 (100%)	11 (100%)	9	16	7 (44%)	7 (44%) ^{+3*}
Group B	95	17 (40%)	36 (46%)	53 (56%)	31	61	13 (21%)	12 (20%) ^{+3*}
Total	106	24 (44%)	40 (49%)	64 (60%)	40	77	20 (26%)	19 (25%) ^{+6*}

* Includes ongoing pregnancies.

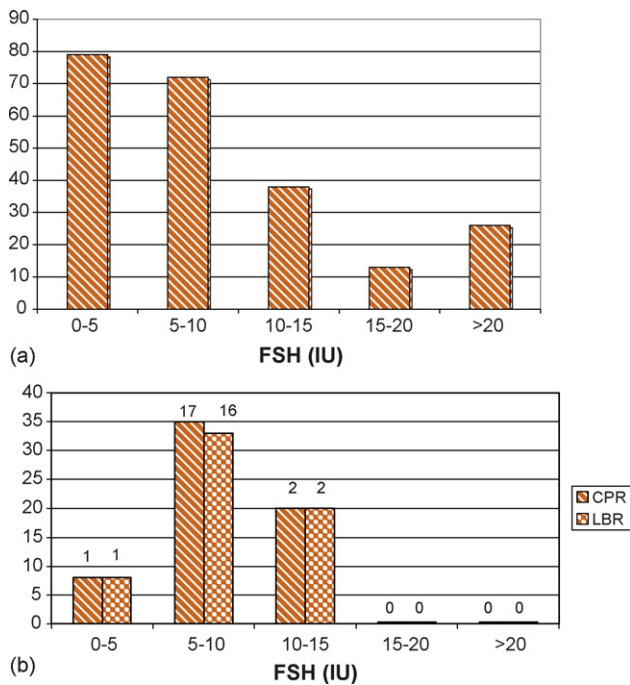


Fig. 1 – (a) Bar chart showing numbers of patients with successful and unsuccessful sperm retrieval for different FSH ranges. (b) Bar chart showing clinical pregnancy rate (CPR), and live birth rates (LBR) per ICSI cycle for different FSH ranges. Absolute numbers of pregnancies and births are written above bars.

out of 72 patients (74%) with an FSH < 10 IU had a successful SSR, which was significantly higher than the 11 out of 34 males (32%) with an FSH > 10, $p < 0.0001$.

Twenty-one males (20%) were found to have testes < 4 cm and FSH > 10 IU, suggesting testicular failure. A significantly lower sperm retrieval rate was seen in this group (29%) compared to 69 men with normal testicular volume and FSH (74%), $p = 0.0001$, as shown in Table 2. In the group of males with raised FSH, there was no significant difference in successful retrieval rates in those with

normal testicular volume and those with small testicular volume, 38% compared with 29%, ($p = 0.71$).

Forty-five out of 106 patients (32%) had clinically distended epididymi, 11 of these were the entire subgroup of patients with CBAVD. Successful sperm retrieval was seen in 24 of the 34 males (71%) in group B and a distended epididymis; 10 (29%) had a positive PESA, 14 had a positive TeSE. The presence of a distended epididymis did not correlate with either a positive retrieval from PESA or TeSE in group B. Other clinical features that are associated with, but not diagnostic of obstruction included four patients with previous infection and 4 with previous surgery. Sperm was successfully retrieved in 5 out of these 8 patients (63%).

Forty patients in total proceeded to ICSI, and a total of 77 cycles were performed. Failed stimulation occurred in four cycles, and the fertilisation rates ranged from 17% to 71%. There were 20 clinical pregnancies, a clinical pregnancy rate (CPR) per cycle of 26%, and only one resulted in miscarriage. There were 15 live births, including 2 twin births, a live birth rate (LBR) per ICSI cycle of 25%, which includes 6 ongoing clinical pregnancies. The CPR and LBR were higher in group A (44% and 44%), compared with group B (21% and 20%), although they were not significantly different, $p = 0.104$ and $p = 0.058$ respectively. The median age of the partner was 31 in both those with and without an obstructive cause. For males with normal FSH and normal testicular volume, the CPR and LBR was 30% and 28%, which includes 6 ongoing clinical pregnancies. This compares with a CPR and LBR of 14% for men with small testes and raised FSH (Table 2), although there was no significant difference between these 2 groups of males ($p = 0.66$ and $p = 0.67$ for CPR and LBR). Clinical pregnancy rates did not correlate with FSH levels as demonstrated in Fig. 1b.

Table 2 – Sperm retrieval rates, clinical pregnancies and live births for clinical subgroups of patients with normal and abnormal FSH or testicular size. Normal testicular size was considered to be ≥ 4 cm, and normal FSH ≤ 10 IU

Clinical subgroup	Number	+ve PESA	+ve TeSE	Adequate sperm retrieved	ICSI cycles	Clinical pregnancies (CPR)	Live birth rate (LBR)
Normal FSH and normal testes	69	24/48 (50%)	29/48 (77%)	53/69 (77%)	61	18 (30%)	17 (28%)*
Increased FSH, normal testes	13	0/5	5/13 (38%)	5/13 (38%)	9	1 (11%)	1 (11%)
Normal FSH, small testes	3	0	0	0/3	0	0	0
Increased FSH, small testes	21	0/1	6/21 (29%)	6/21 (29%)	7	1 (14%)	1 (14%)
Total	106	24/54 (44%)	40/82 (49%)	64/106 (60%)	77	20 (26%)	19 (25%)*

* Includes 6 ongoing pregnancies.

4. Discussion

The development of ICSI and the techniques for sperm recovery has enabled certain azoospermic males to father their biological children. There is, however, limited data available that allows us to adequately counsel such couples as to the success rates of sperm retrieval from SSR. OA and NOA are often used to determine probability of retrieval, but these can only be confidently diagnosed with testicular histology [17]. Testicular biopsy is now rarely performed prior to SSR, so the use of this terminology in the clinical situation can result in inaccuracies when counselling patients. We have divided azoospermic males into subgroups based on clinical parameters so that any clinician can give accurate information when counselling patients for SSR.

FSH, and testicular size are both associated with maturation arrest, and testicular failure [18]. FSH concentration has been shown to be inversely proportional to the spermatogonial population and is associated with NOA [19]. It is, therefore, not surprising that patients in this study with either small testes or elevated FSH had a significantly worse outcome than those with normal parameters. Decreased concentration of inhibin is thought to be responsible for the rise in FSH, and yet increased levels of inhibin have been found in azoospermic patients with elevated FSH [20]. The hormonal relationship with spermatogenesis is certainly not straightforward, with neither FSH, nor inhibin, able to predict successful sperm retrieval [8]. This is manifest by the range of levels of FSH seen in our study, and in particular the successful retrieval in 3 patients with an FSH of over 40 IU. Conversely, men with both normal testicular volume and normal FSH and yet late stage maturation arrest may be clinically indistinguishable from those with rete testis obstruction, particularly as FSH is normal in almost a third of those with defective spermatogenesis [21].

Along with increased FSH, decreased testicular volume is associated with maturation arrest [22] and our data supports this finding. Unsuccessful SSR has been shown to be associated with a significantly lower testicular volume than those with successful sperm retrieval in a population consisting of patients with primary and secondary infertility [8]. One study compared 2 groups of azoospermic males; those with either a raised FSH or small testicular volume, and those with the combination of both [23]. Their retrieval rates were similar to the present study, but there were no comparisons with other subgroups of men with primary azoospermia. The

clinical pregnancy and live birth rates seen in those with small testes and raised FSH compared to those with normal parameters may well reach significance with larger numbers. This may indicate a very poor chance of a successful end outcome for these males embarking on sperm retrieval for ICSI.

It has been suggested that epididymal distension, which is associated with an obstructive aetiology, is predictive of successful SSR [24]. We have shown, however, that epididymal distension is associated with a successful outcome in only 71% of the global patient group. As the overall successful sperm retrieval rate was 60%, epididymal distension is most probably a poor clinical sign of obstruction, and can be misleading. Although this parameter was determined by subjective examination, those categorised as distended for analysis were felt to be grossly distended.

In the clinical setting, it is important to determine if the aetiology of azoospermia is obstructive for two reasons. Firstly, to identify those that would be suitable for reconstruction, for example vaso-epididymostomy, and secondly to give patients a prediction of their likelihood of sperm recovery. As histology is rarely obtained prior to treatment in current practise, there is a need for clinical parameters that can be used to predict the success of SSR. This is especially in light of the emotional and financial implications for both partners that are associated with ICSI. There are factors other than SSR that must enter into counselling, of course, such as details of the ICSI procedure, maternal age and transfer of genetic conditions. There are 37 patients who did not go ahead with retrieval, and it would be interesting to identify factors that have influenced decisions in this group.

In conclusion, azoospermic males presenting with primary infertility should be fully assessed, including serum FSH and testicular size. If testicular histology has not been performed, the terms OA and NOA should be used with caution, and not as predictors of outcome. However, FSH and testicular size can be used to counsel azoospermic males. Those with normal FSH and testicular size can expect high rates of successful SSR, irrespective of whether clinical obstruction is present. However, less than a third of those with small testes and raised FSH will have successful retrieval.

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Editorial Comment

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Bromage et al. correlate testicular size and follicle-stimulating hormone (FSH) levels in men with nonobstructive azoospermia (NOA) with sperm retrieval rates (SRRs), clinical pregnancy rates (CPRs), and live birth rates after intracytoplasmic sperm injection. In contrast to other publications (e.g., including patients with distended epididymis,

history of sexually transmitted disease, etc) [1], the authors use a very strict definition of obstructive azoospermia (OA). Only men with bilateral congenital absence of the vas deferens and those who have undergone vasectomy are defined as having OA. All other patients are defined as having NOA on a clinical basis.

The authors demonstrate clear differences in outcomes within the patient group with NOA; in individuals with normal FSH levels and normal testicular size the SRR and CPR are 77% and 30%

versus 38% and 11% in patients with NOA with increased FSH and normal testicular size versus 29% and 14% in patients with NOA with increased FSH and small testes. I would wish that data collection would be continued to prove if these differences reach the level of significance.

In the literature, we clearly find lower retrieval, fertilisation, and CPRs in NOA and there is consensus that a testicular biopsy should be recommended in these patients [2].

The data in Bromage's paper may develop into a tool for use in counseling patients in the NOA group whether or not to proceed with testicular biopsy. Whereas nomograms have become valuable in

patient information in urologic oncology we still miss a comparable set of data in the field of infertility.

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Editorial Comment

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Azoospermia is found in 10% of male infertility cases and is caused by a testicular insufficiency in the majority of patients. In 20%, a bilateral obstruction of the male genital tract is responsible for the azoospermia.

Through intracytoplasmic sperm injection (ICSI), combined with microsurgical epididymal sperm aspiration (MESA) and testicular sperm extraction (TeSE), biologic parenthood can be achieved for these couples for whom pregnancy used to be impossible.

Nonobstructive azoospermia (NOA) is characterised by hypergonadotropic hypogonadism, in which bilateral small testes and elevated levels of follicle-stimulating hormone (FSH) are found. For the definitive diagnosis of testicular failure a testicular biopsy is needed. This procedure is, however, only performed prior to microsurgery in cases where the testicular volume and FSH level are normal and obstructive azoospermia (OA) is suspected.

Bromage et al. have shown that in 21 men with small testes and an elevated FSH level entering an ICSI protocol sperm could be harvested in just 29% and only one pregnancy resulted. Other studies [1] have similarly poor results in men with severe testicular failure; pregnancies and the live birth rate are usually <10%. ICSI is largely ineffective in these couples.

In counselling these couples prior to sperm retrieval and ICSI it is of major importance that a realistic estimation of the actual chance of success is given and that patients are well informed about the risks of ICSI, including ovarian hyperstimulation, multiple pregnancies, prematurity, low birth weight, and a slightly increased risk of sex chromosomal aneuploidy. Furthermore, multiple testicular biopsies may result in testosterone deficiency requiring lifelong androgen supplementation.

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