

# Cryptorchidism **is associated with** increased risk **of** infertility **and** testicular cancer

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Evidence of cryptorchidism was found in about 10% of our group in more than 1600 infertility patients. The routine semen analyses, as well as basal hormone concentration of FSH, LH and testosterone, differed significantly from those of the healthy semen donors. Only 27.7% of patients with a history of unilateral and 5.4% of patients with a history of bilateral cryptorchidism showed a normal sperm count. Spermatozoa could be found in 13% of patients with unilateral cryptorchidism and in 30% of patients with former bilateral cryptorchidism. The patients that were responding to a conception questionnaire realized that there is a conception rate of 46% in the "non-cryptorchidism-group" and of 21% in the "cryptorchidism-group" ( $p < 0.05$ ). About 20% of patients with testicular neoplasm were previously treated for cryptorchidism. Results of our patient group underline the significance of former cryptorchidism for infertility and testicular cancer.

**C**ryptorchidism represents one of the most prevalent developmental abnormalities in males (Frey & Rajfer, 1982), with a frequency between 0.8 and 1.6% (Sultan, 1997). It is associated with disturbances of fertility (Lee & Coughlin, 2001), testicular neoplasm (Cortes et al., 2001), hernias and torsions (Cilento et al., 1993). Fertility in patients with cryptorchidism may depend upon several factors, such as combination with other genital diseases, whether the cryptorchidism is unilateral or bilateral, degree of maldescensus testis (Hadziselimovic & Herzog, 2001), and especially results and age of correction (Lee & Coughlin, 2001). Men with unilateral undescended testis fathered significantly more children than patients with bilateral undescended testes (Cendron et al., 1989). If the bilateral cryptorchidism remains untreated it

induces azoospermia (no spermatozoa in the semen) in 89% of patients (Hadziselimovic & Herzog, 2001). Cryptorchid boys are born with a reduced number of germ cells which decrease further in the first year of life (Cortes, 1999). This may explain the later impairment of fertility. Development of neoplasia as well as compromised fertility deserves attention in cryptorchid boys. The lifetime risk of testicular neoplasia in cryptorchid boys is about four times higher than that in the general population, amounting to about 3% (Cortes et al., 2001). About 10% of testicular cancer is reported to occur in undescended testes (Johnson et al., 1968). The clinical significance of history in cryptorchidism for testicular neoplasm and male fertility suggested analysis of our infertility patient group. We examined the semen quality of our infertility patients and that of patients with

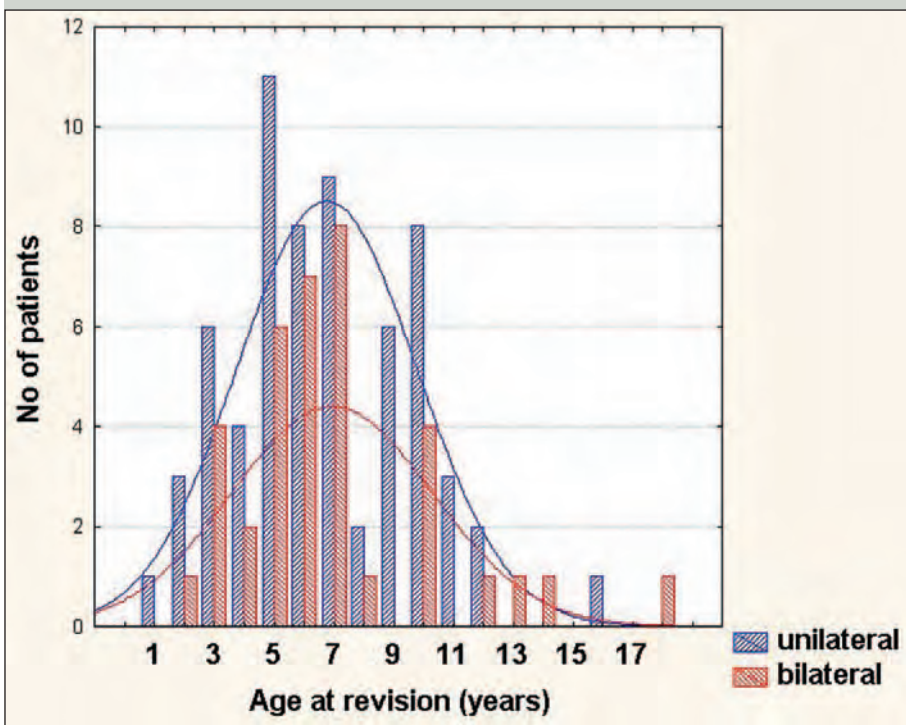


Figure 1 - The age of patients when treated with cryptorchidism

testicular cancer in relation to their history of cryptorchidism, in comparison with a group of healthy semen donors.

### Evaluation role of cryptorchidism in our infertility patients and volunteers

The quality of semen and basal concentration of testosterone, LH and FSH in 167 patients, with a history of unilateral and bilateral cryptorchidism, were analysed after having been selected from 1648 patients with infertility problems. The time of operative revision was determined at  $6.8 \pm 3.3$  years of life (mean  $\pm$  SD, figure 1). In addition, 79 patients with testicular neoplasm referred to our department for cryostorage of semen samples and were screened for former cryptorchidism and analysed. Two hundred and one volunteers not having a history of genital diseases and with normal clinical findings served as the control group. The volunteers were recruited from a screening programme for a clinical study.

Semen samples collected by masturbation after sexual abstinence for 3-5 days were analysed according to the World

Health Organization guidelines (1999) under the quality control programmes of both the European Academy of Andrology and the German Society of Andrology. The measurements of hormone concentration of testosterone, LH and FSH in serum were performed by an immunofluorescence assay of the Delfia system (Pharmacia, Freiburg, Germany). A questionnaire concerning conceptions was sent to the 167 patients with former cryptorchidism ("cryptorchidism-group", CG) and to 374 infertility patients without any previous diseases and with normal clinical findings, who attempted paternity (control or "non-cryptorchidism-group", NCG).

### Increased infertility problems in patients with former cryptorchidism

The data from 1648 infertility patients, aged  $30.8 \pm 6.2$  years (mean  $\pm$  SD, range: 19–62 years), were analysed. The duration of their infertility was  $2.3 \pm 2.1$  years (mean  $\pm$  SD, range: 1–14 years). A history of cryptorchidism was found in 167 patients (10.1 %) of the infertility patient group. One hundred and thirty (77.8%) of the former cryptorchidism group reported unilateral and 37 (22.2%) bilateral cryptorchidism. At the time of consultation the testes of all patients were localized within the scrotum. The 167 patients with former cryptorchidism in their medical history differed in the spermogram parameters of concentration, morphology and motility of spermatozoa as well as in the basal concentrations of FSH, LH and testosterone (Table 1).

Comparison between patients with former unilateral and bilateral cryptorchidism revealed significantly different sperm concentrations and total sperm counts. Thirty six (27.7%) of patients with a history of unilateral and 2 (5.4%) of patients with a history of bilateral cryptorchidism showed normal sperm concentrations, this is more than  $20 \times 10^6$  spermatozoa/ml ( $p < 0.01$ ). The normal total sperm count of more than 40 million /ejaculate revealed 53 (40.8%) of patients with former unilateral and 6 (16.2%) with former bilateral

Characteristics	Infertility patients with former cryptorchidism	Semen donors (Volunteers)
Sperm concentration ( $\times 10^6$ /ml)	$16.0 \pm 2.4$	$96.4 \pm 3.5$ **
Sperm with normal morphology (%)	$10.0 \pm 0.66$	$21.9 \pm 0.5$ **
% progressively motile sperm (WHO grade a)	$17.8 \pm 1.1$	$31.8 \pm 0.9$ **
FSH (U/l)	$12.2 \pm 1.0$	$3.3 \pm 0.1$ **
LH (U/l)	$6.6 \pm 0.6$	$3.6 \pm 0.1$ **
Testosterone (nmol/l)	$15.6 \pm 0.7$	$22.7 \pm 0.3$ **
Azoospermia (% of semen samples)	14.2 %	0 % **

Table 1 - Characteristics of volunteers and patients with cryptorchidism in medical history ( $n = 167$ ), selected from 1648 infertility patients, mean  $\pm$  SEM, \*\* $p < 0.001$ .

cryptorchidism ( $p < 0.01$ ). No spermatozoa (azoospermia) was found in 13.1% of patients (17/130) with former unilateral cryptorchidism and 29.7% (11/37) of patients with former bilateral cryptorchidism ( $p < 0.05$ ). The basal concentration of FSH, LH and testosterone in patients with former unilateral cryptorchidism did not significantly differ from those with former bilateral cryptorchidism. An elevated FSH-concentration ( $>11$  mU/ml) was determined in 62 (37.1%) of patients with former cryptorchidism, in 46 patients (35.5%) with former unilateral and in 17 patients (45.9%) with former bilateral cryptorchidism ( $p > 0.05$ ).

### Patients with former cryptorchidism have an increased risk for testicular cancer

Sixteen (20.3%) of 79 patients with testicular neoplasm referred to our department for cryostorage of semen samples before treatment of testicular cancer were treated for cryptorchidism, either on the side of the testicular neoplasm or on the opposite side. Patients with testicular neoplasm and former cryptorchidism produced significantly less spermatozoa than the cancer patients without a history of cryptorchidism. Furthermore, the patients with testicular cancer showed significantly reduced

Characteristics	Without history of cryptorchidism (n = 63)	With history of cryptorchidism (n = 16)
Sperm concentration ( $\times 10^6$ /ml)	$27.3 \pm 5.0$	$10.7 \pm 7.4^*$
Sperm with normal morphology (%)	$16.1 \pm 1.2$	$12.4 \pm 2.2$
% progressively motile sperm (WHO grade a)	$23.1 \pm 1.8$	$20.0 \pm 5.4$
FSH (U/l)	$11.1 \pm 1.3$	$9.9 \pm 2.4$
LH (U/l)	$5.0 \pm 0.6$	$4.2 \pm 0.9$
Testosterone (nmol/l)	$16.6 \pm 1.0$	$15.4 \pm 2.2$

Table 2 - Characteristics of patients with testicular cancer mean  $\pm$  SEM;

\*  $p < 0.05$ , Mann-Whitney U test

	Non-cryptorchidism group (n = 176)	Cryptorchidism-group (n = 97)
without conception	53.9 %	79.4 % **
spontaneous conception	32.9 %	12.4 % **
conception after IVF	6.9 %	1.0 % *
conception after ICSI	3.5 %	7.2 %

Table 3 - Comparison of conception rates between "non-cryptorchidism" infertility patients and infertility patients with former cryptorchidism (cryptorchidism-group); chi-square-test; \*  $p < 0.05$ , \*\*  $p < 0.01$

sperm counts compared to semen donors (Tables 1 and 2).

### Patients with former cryptorchidism show a decreased pregnancy rate

Questionnaire to patients with and without former cryptorchidism was responded by 97 patients (58.1%) of the "cryptorchidism-group" (CG) and by 176 (47.1%) of the "non-cryptorchidism-

group" (NCG). The spontaneous conception rate in CG was significantly lower than in the NCG-group (Table 3). The total conception rate was 46.1% in the NCG and 20.6% in the CG ( $p < 0.05$ ). The conception rate for patients with bilateral cryptorchidism was not significantly lower than that of the conception rate of patients with unilateral cryptorchidism.

### Comment

Former cryptorchidism is significantly more frequent in infertile than in fertile men (Mieusset et al., 1997) and in a normal population of 1 year of age (Carizza et al., 1990), with a frequency of 2.4% and 1%, respectively. The ratio between unilateral and bilateral cryptorchidism in our patient group corresponded about 3.5: 1. In spite of intensive research and many publications cryptorchidism is still poorly understood (Leissner et al., 1999). Current knowledge suggests a defective influence of a nonandrogenic testicular factor, including Mullerian inhibiting substance (MIS), on the gubernacular outgrowth (Cate et al., 1990). Disturbances of androgen and maternal human chorion gonatotrophine may promote malde-



scensus since the late phase of testicular descent is dependent upon these hormones (Mamoulakis et al., 2002).

Several factors have been identified to play a role for the impaired spermatogenesis.

These include, microdeletions located in different parts of Yg, as reported in 28% of men with a history of unilateral orchidopexy (Foresta et al., 1999), the effect of exposure high temperature, anti-sperm antibodies (Mininberg et al., 1993), a reduced number of germ cells per tubule caused by apoptosis (Dunkel et al., 1997), or by a previously negative influence from the opposite undescended testis or by Sertoli cell degeneration (Cortes, 1999). Reduction of the germ cell population starts in the first year of life (Hadziselimovic & Herzog, 2001). In general infertile population, without a history of cryptorchidism, azoospermia is estimated at 7.7% (Carizza et al., 1990). We found an azoospermia-frequency of 13.1% in patients with treated unilateral cryp-

torchidism. The Johnsen score (Johnsen, 1970) in testicular biopsies yielded further support for a reduced adult fertility of formerly cryptorchid men. Testes, after cryptorchidism, were characterised by a significantly lower histological Johnsen score in testicular tissue, as well as a significantly reduced chance of retrieval of spermatozoa from testicular tissue than patients who had no testicular disease in the past ( $3.7 \pm 2.4$  vs.  $5.9 \pm 2.5$ ,  $p < 0.01$ ) (Glander et al., 2000).

The conception rate is regarded as a superior overall measure of fertility than semen analysis (Lee & Coughlin, 2001). Patients with formerly bilateral cryptorchidism showed a significantly reduced sperm count, but not a significantly lower conception rate, compared to formerly unilateral cryptorchid men. In a larger patient group than ours, Lee and Coughlin (2001) found significant differences in the paternity rates between patients with formerly unilateral or bilateral cryptorchidism.

It is widely accepted that a history of cryptorchidism is an established risk factor for testicular cancer. A lifetime risk of testicular neoplasia of about 3% is four times higher than that in normal population (Cortes et al., 2001). Data in our patient group with testicular neoplasm stresses this association, as 20.1% of the group reported former cryptorchidism. The comparison of sperm counts between the three groups, semen donors, patients with testicular neoplasm and with or without former cryptorchidism (Tables 1 and 2) suggests that testicular cancer (Petersen et al., 1998) as well as the cryptorchidism is associated with impaired spermatogenic function.

Our results concern the association between cryptorchidism, semen quality, conception rates and testicular cancer underline the significance of former cryptorchidism for male infertility and testicular cancer.

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# Reviving the value of reconstructive **surgery** for **obstructive** azoospermic infertility: **is it worth it?**

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For reasons to meet requirements of good medical practice and objectives for cost-benefits featuring the current economy of health care providers, re-constructive surgery; the pelviscopic, urethroscopic, and microsurgery is worth reviving, being competitive with intra-cytoplasmic sperm injection (ICSI), in the treatment of obstructive azoospermia (OA). It provides evidence for a higher diagnostic and comparable therapeutic value in terms of patency restoration 75% and 28% conception achievement. Moreover, it provides evidence and raises demands for redefining the features of obstructive azoospermia, in terms of its diagnostic and therapeutic challenge.

Currently, obstructive azoospermia (OA) is defined and frequently diagnosed by: the absence of spermatogenic cells in the seminal fluid, presence of spermatozoa as well as mature spermatids in the seminiferous tubules of a normal-sized testis, and normal measurement of FSH in serum, due to seminal duct obstruction(1). However not infrequently in non-obstructive azoospermia (NOA), most of the cardinal signs of obstruction; such as the presence of spermatozoa and mature spermatids or both in testicular tissue, normal or moderate testicular volume, and normal FSH in serum, may be demonstrated(2). The obstruction element; therefore seems to provide the sine qua non-defining, diagnosing, and managing OA.

Nonetheless in practice; with the exception of congenital bilateral absence of

the vas deferens and prostatic cysts, the demonstration of the site and-or nature of the obstruction is either absent or limited, due to inherent limitations of current available means for diagnosis (3).

Based on the limited value of the inadequate diagnostic means for obstruction, reconstructive surgery (RCS) often showed limited success, due to inadequate or incorrect approach, explaining recent shift to ICSI(1,4). To date, ICSI has been used successfully in NOA patients, and is currently being advocated for OA, due to its relative success (1,4). However in an era of health care provide economy, to extend ICSI to a potentially correctable state of obstruction, may not meet the objectives in good medical practice (GMP) and cost-benefit demands(5). Recently endoscopic surgery and microsurgery have

gained a wide successful application in female infertility, also condition not yet achieved in male infertility. Among the reasons behind the lag of surgery in male infertility, is the lack of obvious protocols to locate the site of obstruction, and to uncover its pathological nature, in order to provide a greater chance of a successful corrective surgery.

The present work depicts an experience in screening and managing infertile men due to obstructive azoospermia, and investigates the value of reconstructive surgery, through suggested protocols for diagnosis and surgical management.

### Patients and Methods

Forty patients were randomly recruited among males attending the infertility clinic at a private infertility center in Cairo, because of obstructive azoospermia. Each patient fulfilled the inclusion criteria of:

Persistent absence of spermatogenic cells, in at least two consecutive semen analyses each week apart, normal sized testes (> 15 ml), full epididymides, palpable scrotal vasa, presence of spermatozoa as well as mature spermatids in the testicular biopsy or fine needle aspirate, and normal FSH in serum. Further tests aimed at the localization of the site of obstruction included: Trans-rectal ultrasonography (TRUS), quantitative fructose, and a-glucosidase estimation in semen.

#### Diagnostic Surgical Procedures:

Scrotal exploration was performed through a scrotal midline incision under general anaesthesia. Both testes were delivered onto the skin surface. Each vas was dissected out, separated and cannulated through a puncture or 0.5 cm longitudinal incision. Any regressing fluid through the vasal opening was examined microscopically for sperm cells and/or pus cells. Using 18-gauge i.v. cannula, a water-soluble contrast medium (5-10 ml Ultravist, 300, Schering AG) was injected distally, to test patency of the distal seminal duct (inguino-scrotal vas, ampulla, seminal vesicles and ejaculatory ducts),

Obstruction site	Corrective Surgery Type	Patency Rate (n,%)	Conception Rate (n,%)
<b>Single site : (17 , 42.5%)</b>			
Cauda epididymis (10 , 25%)	EV	(8/10 , 80%)	(1/10 , 10%)
Ejaculatory ducts (6 , 15%)	TURED	(5/6 , 83%)	(2/6 , 33%)
Inguinal vasa (1 , 2.5%)	VV, pelvi- scrotal VV	(0 , 0%)	(0 , 0%)
<b>Multiple site : (18 , 45%)</b>			
Cauda-ejaculatory duct (16 , 40%)	Combined EV-TURED	(14/16 , 87%)	(7/16 , 44%)
Cauda-inguinal Vas (2 , 6%)	Combined EV-VV or Combined EV –Pelviscrotal VV	(2/2 , 100%)	(1/2 , 50%)
No-site : (5 , 12%)	EV	(1/5 , 20%)	(0 , 0%)
<b>Total : (n=40)</b>		<b>(30 , 75%)</b>	<b>(11 , 28%)</b>

**Table 1** - Distribution (n,%) of obstruction site, reconstructive surgery type, seminal duct patency and conception rates in patients of obstructive azoospermia (n=40)

EV = epididymo-vasostomy

VV = Vaso-vasostomy

N.B. : All figures are rounded up

TURED = Transurethral resection of ejaculatory ducts

Pelvi-VV = Pleviscrotal Vasovasostomy

either through fluoroscopic screening, or in a vasogram(6). Patency of the proximal seminal duct (proximal portion of the vas and epididymal tubule) was tested by showing sperm cells in saline-wash, and passive flow of the radiopaque medium (passive vaso-epididymogram, Fig.1). Methylene blue dye was used with or in place of the radiopaque medium, whenever radiologic screening was not available, or ejaculatory ducts to be resected.

#### Reconstructive Surgical Procedures:

In patients presenting single-site obstruction at the cauda epididymis; as confirmed by the absence of sperm cells in saline-wash and negative passive retrograde vaso-epididymogram, conventional or microsurgical epididymo-vasostomy (EV) was performed as described before (7).

In patients presenting single-site obstruction at the ejaculatory ducts, as confirmed by non-visualization of the prostatic urethra and presence of sperm cells in the regressing fluid, transurethral resection of the ejaculatory ducts (TURED), and unroofing of the cyst was performed as described before (9).

In patients presenting bilateral multiple-site obstruction at the cauda epididymides and the ejaculatory ducts, simultaneous bilateral EV and TURED were performed.

In patients presenting nonvisualization of the inguinal vas, inguinal vaso-vasostomy (VV) was performed (10), and in case of large-defects of the inguinal vas, pelvi-scrotal VV, using pelviscopy was resorted to as described in our previous work (11).



Figure 1 - passive Flow vaso-epididymogram with ejaculatory duct obstruction

### Follow Up:

All patients who underwent conception and seminal duct patency through semen analysis, were consulted every 3 months following surgery.

### Statistical Assessment:

Frequency was measured using the number of patient's (n) and the percentage of distribution (%).

### Results

Multiple-site obstructions were demonstrated in 45% of patients (18/40) (Table:1). The majority (40%) were combined obstructions at the cauda epididymis and the ejaculatory ducts (16/40), but the inguinal vas in 6% (2/40) (Fig. 2). Single-site obstructions were demonstrated in 42.5% of patients (17/40) (Table:1). The majority (25%) were found at the cauda epididymis

(10/40), the ejaculatory ducts (15%, 6/40)(Fig.1), and the inguinal vas (2.5%, 1/40).

The currently available diagnostic tools in 12% of patients (5/40) could demonstrate no site.

Patency of the seminal duct could be restored by RCS in 75% (30/40), and pregnancy achieved in 28% (11/40) of the patients during the first 12 months following surgery (Table:1).

Patients proved to have combined caudal and ejaculatory ducts obstruction showed higher frequency of restoring seminal ducts patency (87%, 14/16), higher scores of seminal fluid fertility parameters ( $\geq 20$  million / ml,  $\geq 40\%$  1 h motility) and a higher frequency of conception (44%, 7/16) (Table:1).

The second most successful RCS was demonstrated for single-site obstructions at the cauda epididymis, restoring patency in 80% (8/10). Achieving a sperm count of  $\geq 15$  million / ml, 1 h motility  $\geq 30\%$ , but pregnancy in 10% (1/10), the ejaculatory ducts in 83% and 33% consecutively, with a sperm count of  $\geq 10$  million/ml, and 1 h motility  $\geq 20\%$ .

RCS for single site obstruction at the inguinal vasa did not restore patency in the single case investigated. On the other hand, combined obstruction at the cauda and inguinal vasa could be cor-

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rected by combined EV-VV or pelvi-VV resulting in patency restoration in all (100%, 2/2), and pregnancy in one patient, representing 50% (1/2) (Table:1, Fig. 3). In five patients; however the site of obstruction could not be demonstrated, for whom bilateral EV resulted in patency with no conception in one patient (Table 1).

### Discussion

Among the cardinal features of OA, obstruction seems to form the single crucial differentiating element. Being specific and least prone to overlapping, compared with other clinical, laboratory or histopathologic features, the obstructive element should be defined and screened for all diagnostic protocols. Consequently, challenges in the reconstructive surgical protocol; in terms of failure or success, will determine the cost-effectiveness and cost-benefits acceptable to patients, insurers and population.

Present work provides evidence supporting the value of intraoperative imaging in the demonstration of the obstructive element alongside the distal seminal duct, and proximal vaso-epididymal duct (Table1). Intraoperative fluoroscopic screening, and vasograms provide relatively sensitive and specific tools for the diagnosis of obstruction compared with other clinical, biochemical, ultrasonographic and histopathologic tools(3,6,9,12). ICSI, however doesn't offer such diagnostic tools to fulfill the requirements for GMP and cost-effectiveness. Moreover planning for scrototomy in the course of RCS offers a chance for simultaneous diagnostic and treatment procedures aimed at maximizing the cost-effectiveness and cost-benefits of RCS.

Likewise, vasography allowed the demonstration of combined obstructions in the majority of patients (46%) most of them were at the cauda epididymis and ejaculatory ducts (40%). Thus it allowed for a successful restoration of patency in 87%, with satisfactory semen parameters leading to conception in 44% of the patients. ICSI however

does not correct obstruction and the conception rate is nearly comparable (18%-41%)(5). Except for a single patient with obstruction at the inguinal vasa. Single-site obstructions were likewise appropriately demonstrated and properly managed by RCS, leading to comparative success rate in terms of patency restoration, seminogram improvement and conception rate in patients with obstruction at the Cauda (80%, 10%) and ejaculatory ducts (83%, 33%) (Table:1).

However for OA, the absence of consensus in protocols for diagnosis and treatment and the heterogeneity of the etiology behind obstruction and the inclusion criteria may explain the conflicting results with other works (12).

To recommend, the failure to demonstrate the site of obstruction in 12% of patients raises demands to find tools to screen the seminal duct proximal to the Cauda epididymis (proximal epididymal tubule, vasa efferentia, rete testis and seminiferous tubules), to explain the etiopathogenesis of partial obstructive azoospermia, and intermittent azoo-oligozoospermia.



Figure 1 - passive Flow vaso-epididymogram with ejaculatory duct obstruction



Figure 1 - passive Flow vaso-epididymogram with ejaculatory duct obstruction