

# Male infertility in Kuwait

## *Etiologic and therapeutic aspects*

Laila R. Qadan, MD, Adel A. Ahmed, MD, Kusum A. Kapila, MD, FRCPath, Nabida A. Hassan, MD, MRCOG, Jan A. Kodaj, MD, PhD, Shabed K. Pathan, MD, MBBS.

### ABSTRACT

**Objectives:** To evaluate the pathological patterns associated with male infertility in Kuwait and to characterize treatment outcome after varicocele repair using percutaneous varicocele embolization.

**Methods:** We carried out a prospective study of 64 infertile men in Kuwait between 2001 and 2005. All patients included had proven non-obstructive azoospermia or oligospermia (sperm count <20 million/ml). All patients underwent ultrasonographic evaluation of the scrotum. Fine needle aspiration of the testes was performed on all azoospermic patients.

**Results:** A total of 24 (38%) patients were azoospermic while 40 (62%) were oligospermic. Sertoli-cell-only pattern was the most common cytopathology associated with primary testicular failure. Among the oligospermic patients, 50% had small to moderate varicocele. Spermatic vein embolization resulted in a significant rise in the mean sperm count from  $10.6 \pm 3.8$  million/ml to  $30.2 \pm 6.8$  million/ml ( $p < 0.05$ ) in 5 treated oligospermic patients, followed by spontaneous pregnancy in 2 couples. No effect was seen on azoospermic patients.

**Conclusion:** From an etiological point of view, we believe that the high incidence of Sertoli cell-only syndrome among nationals and residents of a country that underwent a major environmental insult strengthens the chances of an environmental role in the development of this syndrome. From a management point of view, in cultures where in vitro fertilization is either still not widely acceptable or is unaffordable, oligospermia with clinical or subclinical varicocele deserves a trial of a low risk, out patient procedure, namely, spermatic vein embolization that could improve fertility.

*Saudi Med J 2007; Vol. 28 (1): 96-99*

*From the Departments of Medicine-Endocrinology (Qadan), Departments of Radiology (Ahmed), Departments of Pathology (Kapila), Faculty of Medicine, Kuwait University, Maternity Hospital (Hassan), Departments of Radiology (Kodaj), Departments of Pathology (Pathan), Mubarak Al-Kabeer Hospital, Ministry of Health, Kuwait.*

*Received 10th June 2006. Accepted 13th September 2006.*

*Address correspondence and reprint request to: Dr. Laila R. Qadan, PO Box 39168, Nuzha 73052, Kuwait. Tel. +965 9441222. E-mail: Lailaqadan@hotmail.com*

Male infertility has been studied extensively over the years. The role of environment with its noxious factors in the etiology of male infertility has been suggested in many reports.<sup>1-5</sup> Examples include the effect of drinking water in Paris,<sup>1</sup> and the exposure to nuclear radiation and working in hot conditions, among military personnel.<sup>6</sup> The Gulf war in 1990 resulted in a major environmental insult secondary to oil well fires, and oil spill. Both air and drinking water were negatively affected.<sup>7,8</sup> Environmental pollution was blamed for the increased incidence of congenital heart disease and spontaneous abortion in Kuwait post the gulf war.<sup>9,10</sup> In this study, we aim to shed some light on the possible negative effect of environment on spermatogenesis among Kuwaiti males through assessing the underlying pathological patterns associated with male infertility.

Public's opinion towards childlessness and its therapy is greatly affected by cultural and socioeconomic status. Internationally, different modalities of therapy have been tried with variable results in improving fertility.<sup>11-17</sup> Kuwait is an Arab country with a significant imported working power population. Assisted reproductive techniques (ART) are available in Kuwait both in public and private hospitals. While they are offered free of charge to Kuwaitis in public hospitals, the waiting list is extremely long let aside the negative social stigma associated with their use. Furthermore, most of the foreign workers, have low-paid jobs, thus cannot afford ART at private hospitals. Since varicocele is clearly related to sub-fertility, its treatment could improve fertility rates.<sup>12-18</sup> With the availability of spermatic vein embolization (SVE) as an outpatient, low morbidity procedure that proved to be equally effective in clinical and subclinical varicocele in improving semen

characteristics,<sup>14-17</sup> we conducted this study to assess the efficacy of SVE in a subpopulation of infertile men with ultrasonic- proven varicocele. The study highlights a multidisciplinary approach to male infertility involving endocrinology, pathology, radiology, obstetrics and gynecology.

**Methods.** In this prospective study carried out in an endocrinology clinic at a university-based hospital in Kuwait, patients were enrolled (between 2001-2005) if they satisfied the following inclusion criteria: 1. age >20 years, 2. sperm count <20 million/ml on at least 2 occasions, 3. infertility for at least 2 years, 4. normal female spouses as judged by a senior gynecologist. Patients with a history of trauma or surgery on their genital organs were excluded. An informed consent was obtained from each patient. Patients were evaluated according to a pre-established protocol, which included a detailed history regarding smoking, alcohol intake, sexually transmitted disease, hepatitis, diabetes, hypertension and hyperlipidemia. Accordingly, 64 otherwise healthy patients with either non-obstructive azoospermia, or oligospermia were included in the study. All patients had a general chemical profile, thyroid function, serum prolactin, testosterone, leutenizing hormone (LH), and follicle-stimulating hormone (FSH) levels done at baseline. All patients underwent scrotal color duplex ultrasonography regardless of the clinical evidence of varicocele. Invasive procedures were carried out after obtaining an informed consent of every patient.

The data was analyzed using Statistical Package for Social Sciences (SPSS, Chicago, IL) software. Sperm counts were analyzed using Wilcoxon-signed rank test. A *p* value <0.05 was considered significant

Scrotal color duplex ultrasonography was performed using Logic 500 (GE Medical Systems, Milwaukee, WI) ultrasound unit and a 7.5-MHz linear array transducer. The test was carried out in both supine and standing positions, with and without Valsalva maneuver. Diagnostic criteria used to define varicoceles were as described by Eskew et al.<sup>19</sup>

All azoospermic patients underwent fine needle aspiration of the testes. Under aseptic conditions, the testis was positioned with the epididymis directed posteriorly, the scrotal skin was stretched and wrapped behind the testis. Fine needle aspiration was performed percutaneously with a 23 gauge, 1 inch fine needle using precise, gentle, in and out movements, varying from 5-8 mm. Five to 10 needle passes were made at each testis. Tissue fragments were then expelled and smeared onto slides and allowed to air dry. The smears were subsequently stained by the May Grunwald Giemsa stain.

Patients with varicoceles, who opted to undergo an intervention before considering ART (N=19), were referred for percutaneous SVE. Under sterile conditions, the right common femoral vein was accessed following Seldinger technique. Selective catheterization of the left renal vein and internal spermatic vein (ISV) was carried out using an end hole 4Fr Glide Cobra 2 catheter (Terumo Medical Corporation-Tokyo, Japan). The catheter tip was placed close to origin of ISV and venography was obtained, with non ionic contrast (Iohexol, 240 mgI/ml, Amersham Health, Cork-Ireland), while the patient performed Valsalva maneuver. A long, 5-Fr, super Arrow Flex sheath (Arrow International, PA, USA) was placed with the tip engaging the orifice of ISV to provide and maintain stability during coaxial catheterization and embolization. The Cobra catheter was advanced distally to a level just above superior pubic ramus, where the first coil was deployed (MREYE embolization coil, William Cook, Bjaeverskov, Denmark). Then multiple coils were placed to "pack" or "nest" the ISV and its tributaries (with the patient performing valsalva maneuver). Care was taken not to deploy coils in the renal vein. Repeated contrast injections were made during the course of embolization to monitor progress of thrombosis. After complete thrombosis was documented, the catheter and sheath were removed and homeostasis was achieved by manual compression for 10 minutes. Gonadal shielding was routinely applied and fluoroscopy time was kept to the minimum possible. Minimal sedation with Medazolam and Fentanyl was required. The procedure was well tolerated with no complications. Sperm count was repeated 3 months after the procedure and a 6 months clinical follow up was carried out to check for spontaneous pregnancy.

**Results.** Sixty-four patients (mean age, 32.5 years; range, 22-46 years) satisfied the inclusion criteria. A total of 43% were Kuwaitis, 42% were smokers. None had comorbid conditions. All patients claimed normal libido and sexual activity. Eighty-six percent had primary infertility while 14% had secondary infertility.

Twenty-four (38%) patients had azoospermia. Cytological patterns and hormonal levels are shown in Table 1. Sertoli cell-only- syndrome seems to be the major cause of primary testicular failure constituting 58% of the cases (14 patients). Thirty-eight percent of non obstructive azoospermia was secondary to maturation arrest or hypospermatogenesis or both. One patient had testicular atrophy. Three azoospermic patients had coexisting varicocele, spermatic vein embolization in these patients did not change their semen analysis or the cytological features of testicular biopsy which was repeated 3 months after the procedure.

Forty (62%) patients were oligospermic. Half of these (50%) had mild to moderate varicocele, mostly left sided, documented on color-doppler sonography. Twenty percent had hormonal abnormalities (hypogonadotropic hypogonadism, prolactinoma or hypothyroidism). The remaining 30% had idiopathic oligospermia. Patients with varicocele and those with idiopathic oligospermia had no significant difference in FSH and LH levels, which were within normal ranges.

Of the 16 oligospermic patients who underwent SVE, 5 showed a significant increase in sperm count at 3 months follow up. Mean sperm count ( $\pm$ SD) increased from  $10.6 \pm 3.8$  million/ml to  $30.2 \pm 6.8$  million/ml ( $p=0.039$ ). This was not associated with a significant change in sperm morphology or motility. There were no complications associated with the procedure. Two couples reported spontaneous pregnancy during the 6 months follow up. In comparison, patients with idiopathic oligospermia exhibited no significant change in any of the semen parameters at 3 or 6 months follow up.

**Discussion.** Chronological deterioration in levels of male reproductive parameters, even among animals, has been reported.<sup>1,20,21</sup> Adverse environmental factors are most likely to blame. For example, the decline in the concentration of sperms and the quality of semen during the past 20 years in Paris has been described by Auger et al<sup>1</sup> and has been attributed possibly to environmental pollution or water supply. Chronological changes in the histopathological distribution of primary testicular failure seem to be happening too. When comparing data from North America; in the 1970's primary defects of the testes were mainly attributed to hypospermatogenesis and maturation arrest, while the report of Jarow et al<sup>25</sup> in 1989 revealed a change in favor of Sertoli-cell-only syndrome.<sup>22-25</sup> A high frequency of Sertoli cell-only-syndrome has been also reported in Saudi Arabia in 1995 and in Japan in 2001.<sup>2,26</sup> In accordance with this seemingly universal incline in the incidence of Sertoli cell-only-syndrome, our results were not surprising.

Kuwait was faced with a major environmental offence following the Gulf War.<sup>7,8</sup> Examples include oil well fires, oil spills, top layer soil contamination with crude oil and its combustion products which in turn polluted underground drinking water.<sup>7,8</sup> The increased prevalence of this syndrome, as a subcategory of a relatively high percentage of azoospermia, among nationals and residents of an environmentally challenged country could be supportive of a detrimental role of the noxious surrounding in its etiology. Since our sample was small, we reviewed all testicular biopsies carried out over the last 5 years at the pathology department of our hospital, which is a major referral center from all areas of Kuwait. A total of 278 biopsies demonstrated testicular hypofunction, out of these 166 cases (60%) showed Sertoli cell-only-syndrome, confirming our observation on a larger sample group.

In agreement with Silber<sup>11</sup> and Jarow et al<sup>25</sup>, our data support the notion that the inverse relationship between FSH and spermatogenesis is not always perfect. This was evident in few patients with azoospermia secondary to maturation arrest without an elevation in FSH. In other words, normal FSH in the face of azoospermia does not always indicate normal spermatogenesis or obstruction.

There is little doubt that there is an increased incidence of varicocele in infertile males,<sup>18,27</sup> however, there is considerable debate as to the efficacy of intervention.<sup>12-17,27-32</sup> Available data suggest that even in patients with azoospermia and severe oligoasthenospermia, varicocele repair induces spermatogenesis and achieves pregnancy<sup>17,27</sup> or at least improves intrauterine insemination success rates.<sup>28</sup> Percutaneous SVE is an effective, safe, nonsurgical method of obliterating varicoceles.<sup>14-17,33</sup> It is an outpatient procedure associated with a low morbidity rate and has proved effective in improving spermatogenesis and achieving subsequent pregnancy.<sup>14-17</sup> In accordance with available experience, SVE was offered to all patients with proven varicocele in our study. Most patients favored the procedure as an initial step before considering in-vitro fertilization (IVF). This may reflect cultural values that could guide therapeutic

**Table 1** - Mean values  $\pm$ SD of FSH, LH and testosterone levels in relation to cytology associated with azoospermia.

Cytology/Hormones	FSH (1-9 IU/L)	LH (3-13.5 IU/L)	Testosterone (8-35 nmol/L)
Sertoli cell-only-syndrome (N=14)	24.7 $\pm$ 6.7	4.9 $\pm$ 1.4	16 $\pm$ 4.2
Atrophy (N=1)	32	16	6
Maturation arrest/ hypospermatogenesis (N=9)	11.3 $\pm$ 5.4	5.3 $\pm$ 1.4	16.6 $\pm$ 2.2

SD - standard deviation, FSH - follicle stimulating hormone, LH - leutenizing hormone

options. Among Arab males self image is greatly affected by fertility and potency and IVF continues to be less socially acceptable than the western world. This is supported by the observation that none reported loss of libido or erectile dysfunction even those with subnormal testosterone levels. Furthermore, for expatriates who could not afford IVF, SVE seemed to be the only option. In our study, oligospermic patients showed similar but less dramatic response than previously reported with varicocele repair.<sup>13,15</sup> On the other hand, unlike other reports, azospermic patients showed no significant change in spermatogenesis after the repair.<sup>17,27</sup> In both situations it was most likely related to a smaller sample size. From our limited experience, we believe that SVE is a feasible, affordable (at least at our center) option that could help some infertile couples in achieving pregnancy, especially if varicocele was the only demonstrable abnormality.

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