



Genital Operations and Male Infertility: Is Inguinal Hernia a Component of Testicular Dysgenesis Syndrome?

Omu*, Al-Azemi MK, Omu FE, Mohammed AT and George S

Abstract

Background

Testicular Dysgenesis Syndrome encompasses a constellation of conditions like, Cryptorchidism, Hypospadias and Testicular Cancer and associated with poor sperm quality. Objective of the study is to evaluate the association between the genital disorders cryptorchidism, hypospadias and hernia, and male fertility, association with Testicular Dysgenesis Syndrome.

Patients and Methods

Men referred with male infertility and found on clinical evaluation to have had history of inguinal hernia, cryptorchidism and hypospadias and had corrective surgery form the subjects of the study. The study period was 10 years from January 1, 2001 to December 31, 2010. All patients had investigative semen analysis according to WHO guidelines and hormone profile including FSH, LH, Prolactin and Testosterone.

Results

During the study period, there were 2251 patients seen at the infertility clinic. Out of these 115 (5.1%) had history of genital operations: 87 had prior history of inguinal hernia, 21 had cryptorchidism, 5 had hypospadias and 2 had testicular cancer. All the 6 men (28.6%) who had orchidopexy in the prepubertal period (before 9 years of age), had normal sperm parameters and normal testosterone of above 10 nmol/L, but nine (42.9%) who had orchidopexy after puberty (after 9 years) had moderate to severe oligozoospermia. The remaining 6 (28.6%) had testicular atrophy, non-obstructive azoospermia and low testosterone levels. Similarly, 26 (29.9%) of the patients with herniorrhaphy, had azoospermia, testicular atrophy and low serum testosterone.

Conclusion

Genital disorders and corrective operation are associated with poor sperm parameters. In view of the congenital origin of inguinal hernia, it may be part of the Testicular Dysgenesis Syndrome.

Keywords

Testicular Dysgenesis Syndrome; Cryptorchidism; Hypospadias; Testicular cancer; Male infertility

Introduction

Infertility is the inability of a sexually active, non-contraception couple to achieve spontaneous pregnancy in one year according to World Health Organization [1]. Concise and up-to-date information regarding the contemporary epidemiological characteristics, clinical features and pathophysiological impacts of these common abnormalities on male fertility is crucial for the healthcare provider to identify the best treatment option or prevention [2]. Male fertility can be reduced as a result of factors which include malignancies, urogenital tract infections, increased scrotal temperature (e.g. varicocele), endocrine disturbances, genetic abnormalities and immunological factors and congenital or acquired urogenital abnormalities [1,3]. Some of these structural abnormalities might damage or block blood supply to the testes, epididymis, seminal ducts or other reproductive structures and can ultimately decrease fertility [2].

In 2001, a Testicular Dysgenesis Syndrome (TDS) was first described encompassing poor semen quality, undescended testis, hypospadias and testicular cancer [4] as symptoms of one underlying entity. The hypothesis of Testicular dysgenesis syndrome proposed that the four conditions cryptorchidism, hypospadias, impaired spermatogenesis and testis cancer may all be manifestations of disturbed prenatal testicular development in intrauterine period [5]. Cryptorchidism and hypospadias are common genital birth defects that affect 2-9% and 0.2-1% of male newborns, respectively with large geographic variation, and in several countries increasing trends have been reported. Both conditions share many risk factors, and they are also interlinked to the risk of testis cancer and poor semen quality [6]. The etiology of TDS is suspected to be related to genetic and/or environmental factors, including endocrine disrupters and phthalates [5,7]. Cryptorchidism or undescended testis is one of the most common anomalies encountered in pediatric urology and is estimated to affect 1 to 4 per cent of full term and up to 30 per cent of preterm male neonates. The descent of the testes during development is controlled by insulin-like 3 peptide and steroid hormones produced in testicular Leydig cells, as well as by various genetic and developmental factors [8,9]. The associated problems of sub-fertility or infertility and malignant transformation have been recognized for long. Fertility is impaired after both unilateral and bilateral cryptorchidism [10].

Hypospadias is a birth defect in which the urethra opens on its underside instead at the tip. It is believed that this is associated with male infertility, since the urethra carries semen out of the body. It occurs in up to 4 in 1000 newborn boys [11,12]. Conversely, there is evidence that hypospadias and impaired spermatogenesis can be classified as TDS if combined with cryptorchidism because recent studies have shown that men with isolated hypospadias, only a fraction of cases are linked to TDS and impaired spermatogenesis [6].

Testicular Cancer (TC) has multifactorial etiologies, such as Hypospadias, cryptorchidism and inguinal hernia [13-15]. About 10% of all cases of testicular germ cell tumors (TGCT) occur in men with a history of cryptorchidism [14]. It is well documented that rare genetic abnormalities which cause testicular dysgenesis (e.g. 45 X/46XY and androgen insensitivity) are associated with a high risk of testicular cancer, often in combination with undescended testis

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and hypospadias [16]. In addition, there is increasing biological and epidemiologic evidence that some infections and infectious agents and other inflammatory mechanisms might increase the risk of TC [17-19]. From the foregoing, several epidemiological studies have shown that conditions like cryptorchidism, impaired spermatogenesis, hypospadias and testicular cancer can be associated as risk factors for each other. Dysgenesis has been demonstrated in biopsies of the contralateral testis of men with testis cancer and in infertile men [20].

Galen in 176 A.D was the first one to describe the pathogenesis of indirect inguinal hernia when he described the processus vaginalis as "The duct descending to the testicle is a small offshoot of the great peritoneal sac in the lower abdomen (processus vaginalis peritonei) [21]. The factors responsible have not been fully elucidated. This is as a result of paucity of research on the association between inguinal hernia and male infertility. On the other hand, the medical literature is replete with the serious impact of hernia repair-herniorrhaphy/hernioplasty on sperm parameters and thus male fertility. More than half of all men who underwent inguinal repair as children had serum antisperm antibodies and low sperm counts, both conditions are associated with decreased fertility [22-24].

Objective of the study is to evaluate [1] the association between the genital disorders cryptorchidism, hypospadias and hernia, and male fertility. To adduce evidence to support the hypothesis that hernia is a component of Testicular Dysgenesis Syndrome [2].

Patients and Methods

Infertility is the inability of a sexually active couple and without use of contraception, to achieve pregnancy in one year. Primary infertility means failure to achieve a first pregnancy, 'secondary' infertility means failure to achieve a subsequent pregnancy.

At the Maternity Hospital, Kuwait, we have been running a combined infertility since 1995, in which we see both the woman and her husband together at the first consultation. Both of them have clinical evaluation which includes history, physical examination and investigation of their infertility problem. Men referred with male infertility or found on clinical evaluation to have had history of inguinal hernia, cryptorchidism and hypospadias form the subjects of the present study for 10 years from January 1, 2001 to December 31, 2010.

Ethical consideration

Verbal informed consent was received from all the men and the study was approved by the Institutional Review Board of the Maternity Hospital, Kuwait. To obtain the participants' informed consent, the objectives and general procedures of the research were explained to them as well as their right to drop out at any given moment with no ensuing change in the quality of the medical care they would continue to receive.

Clinical Evaluation

Clinical evaluation was carried out in all the men namely full medical and surgical history. In the physical examination, the weight (wt) was measured in kilograms and height (ht) in meters for the purpose of calculating the body mass index (BMI =wt in kilogram /ht in meter². Other examinations included Blood pressure and evaluation of respiratory and cardiovascular systems. Abdominal examination was carried out to exclude abdominal mass, incisional, inguinal and femoral hernias. External genitalia were examined for descent of the testes, and orchidometry was done. We used the beads

which are compared with the testicles of the patient, and the volume is read off the bead which matches most closely in size. Prepubertal sizes are 1-3 ml, pubertal sizes are considered 4 ml and up and adult sizes are 12-25 ml. The cut-off point of <10 ml was used as testicular atrophy.

Semen analysis

All patients had investigative semen analysis according to WHO guidelines [1], namely after three days sexual abstinence, and collected by masturbation method and analyzed within one hour of specimen collection using the Haemocytometer, an instrument for visual counting of the number of cells in a blood sample or other fluid under a microscope.

Definitions of the sperm parameters after Semen analysis according to WHO guidelines [1]

Normozoospermia is when semen shows normal characteristics in a seminogram. The volume of the ejaculate or sample must be 2-5 ml, it must contain over 15 million sperm/ml, 32 % of which must have good motility and at least 4% must look normal.

Oligozoospermia, refers to semen with a low concentration of sperm of less than 15 million sperm in the semen per ml.

Azoospermia is the medical condition of a man not having any measurable level of sperm in his semen.

Asthenozoospermia is when the percentage of mobile sperm in the semen is less than 32%.

Teratozoospermia, also known as teratospermia, is a semen alteration in which there are a large number of spermatozoa with abnormal morphology.

Leucocytospermia is a condition of a high white blood cell count in semen is typically over one million leukocytes per ml.

Laboratory investigations

Similarly, all patients had hormone profile of FSH, LH, Prolactin and Testosterone, using radioimmunoassay.

Statistical Methods

We analyzed fully completed questionnaires only. We tested comparisons with the Wilcoxon Rank Sum, proportions by Chi Square. We report results as mean (SD) or median (range). The correlation among variables, where appropriate used the Pearson lineal correlation coefficients, significant correlation was considered at significance level < 0.05).

Results

During the study period, there were 2251 patients seen at the infertility clinic. As shown in Table 1, there were 115 (5.1%) with genital operations, with the composition 87 (76%) had prior history of inguinal hernia, 21 (18.3%) had cryptorchidism, 5 (4.4%) had hypospadias and 2 (1.7%) had Testicular cancer that was treated with chemotherapy. The mean age was 34.8 ± 6.4 years, 21 % were below 30 years and 6 percentage above 50 years, 34 % were smokers and more men were with primary infertility than secondary (p<0.01). Of the 39 smokers, 36 (41.4 %) had history of hernia and remaining 3 (14.6 %) were men with history of orchidopexy, thus more men with hernia were smokers (p<0.01).

Table 1: Demographic Characteristics.

Item	Number	Percentage
Age (years)		
≥ 30	24	20.9
31-40	58	50.4
41-50	26	22.6
> 50	7	6.1
Smoking Habits		
Non-smoking	76	66.1
Smoking	39	33.9
Type of Infertility		
Primary	84	73
Secondary	31	27
Types of Genital disorders		
Inguinal hernia	87	75.6
Cryptorchidism	21	18.3
Hypospadias	5	4.4
Testicular cancer	2	1.7

As shown in Table 2, patients with hernia, cryptorchidism, Hypospadias and testicular cancer had similar sperm parameters. Hernia was associated with lower sperm concentration ($p < 0.05$), progressive motility ($p < 0.05$) and significantly higher azoospermia ($p < 0.01$) compared to men with history of cryptorchidism or hypospadias. However, hernia/herniorrhaphy was more significantly associated with azoospermia, testicular atrophy and low testosterone when compared to men with cryptorchidism or orchidopexy ($p < 0.05$). In the present study, all the 6 men (28.6%) who had orchidopexy before five years of age, had normal sperm parameters and normal testosterone of above 10 nmol/L, but nine (42.9%) who had orchidopexy after five years of age had moderate to severe oligozoospermia. The remaining 6 (28.6%) had testicular atrophy, non-obstructive azoospermia and low testosterone levels. Similarly, 26 (29.9%) of the patients with herniorrhaphy, had azoospermia, testicular atrophy and low serum testosterone.

In Table 3, sperm parameters are compared between men that manifested or had diagnosis of hernia in early age up to prepubertal period (below 9 years) and those in adult age. Diagnosis of hernia in prepubertal period was associated with higher sperm concentration ($p < 0.05$), Sperm motility ($p < 0.05$), Hypo-osmotic swelling test ($p < 0.05$) and lower non-motile sperm (asthenozoospermia) ($p < 0.05$), lower sperm count (oligozoospermia) and sperm with abnormal morphology ($p < 0.05$) and azoospermia ($p < 0.05$) than if the diagnosis was made in adulthood. Almost the trend is revealed by the timing of herniorrhaphy, except with HOS. Men that had diagnosis of hernia or their hernia repaired at an early age had significantly better sperm parameters ($p < 0.05$) and fewer men with azoospermia, testicular atrophy and low testosterone ($p < 0.01$). Smokers who had hernia were significantly associated with asthenozoospermia ($p < 0.01$) and leucocytospermia ($p < 0.001$).

As shown in Table 4, all the 26 men with azoospermia had high LH and FSH (28.4 ± 6.4 and 50.4 ± 12.2 IU/L, respectively) and low testosterone in range of Testicular failure ≤ 5 nmol/L. Strong Correlation between high LH (≥ 28 IU/L) and low testosterone (5 nmol/L), $r = 0.672$. All the men with testicular atrophy and Azoospermia.

Discussion

The present study has demonstrated that hernia/herniorrhaphy, cryptorchidism, Hypospadias and testicular cancer are associated with impaired sperm quality, even after reparative surgery, especially with associated azoospermia and low serum Testosterone. Hernia repair was associated with impaired sperm parameters in form of azoospermia, oligozoospermia, asthenozoospermia and leucocytospermia. A number of studies have evaluated the fertility after herniorrhaphy [22-25]. In a study involving 8500 patients attending the fertility clinic due to infertility, 565 men (6.65%) reported an incidence of inguinal hernioplasty with or without subsequent atrophy of the testis. In cases where hernioplasty was followed by atrophy of the testis, damage to sperm characteristics and Sertoli cell function was found to be far greater. The reasons for testicular damage may be due to ischaemic orchitis or immunological reactions [22]. The sperm impairment was worse if the diagnosis of hernia and hernia repair were made in adulthood compared to at adolescence or earlier. This was probably due to trauma, especially compromise of blood supply to the testes. In contradiction, some clinical studies showed lack of adverse impact on male fertility in humans with inguinal hernias [23,24]. More than half of all men who underwent inguinal repair as children had impaired sperm parameters as a result of serum antisperm antibodies and low sperm counts, both conditions are associated with decreased fertility [23]. We strongly believe that the difference may as result of trauma at hernia repair which is predicated on the experience of the surgeon. A good number of the men with hernia probably had incarceration and strangulation, in which part of the herniated intestine becomes twisted or edematous and causing serious complications, possibly resulting in intestinal obstruction and necrosis. This could interfere with normal blood flow and peristalsis, and leading to intestinal obstruction and necrosis, resulting in an urgent need for surgical intervention.

Moreover, 41.4 percent of our patients with hernia were smokers, a condition known to have deleterious effect on sperm parameters [26,27].

In the present study, all the 6 men (28.6%) who had orchidopexy before five years of age, had normal sperm parameters and normal testosterone of above 10 nmol/L, but nine (42.9%) who had orchidopexy after five years of age had moderate to severe oligozoospermia. The remaining 6 (28.6%) had testicular atrophy, non-obstructive azoospermia and low testosterone levels. This is in agreement with the findings of a recent review article [23]. The timing of orchidopexy is therefore an important reflection of the status of sperm parameters. In a recent epidemiological study in the UK has demonstrated that in the period between 2001 and 2008 the prevalence of cryptorchidism at birth was 5.3% for full-term infants, and 14% for preterm infants [22]. However, recent studies have demonstrated that among men with isolated hypospadias, only a fraction of cases are linked to TDS and impaired spermatogenesis [28]. Testicular cancer risk is 37-63% higher in males with inguinal hernia and 88-141% with hypospadias in a meta-analysis and large cohort-study. Studies in the United Kingdom have indicated an elevated risk of TC in patients with a history of sexually transmitted disease or Neisseria gonorrhoeae infection [29-31].

Is hernia a component of Testicular dysgenesis Syndrome?

Since 176 AD when Galen demonstrated that indirect inguinal hernias usually occur because of a persistent processus vaginalis, an embryonic developmental out-pouching of the peritoneal cavity

Table 2: Effects of Genital Operations on Sperm Parameters.

Sperm Parameters	Hernia N=87	Cryptorchidism N=21	Hypospadias N=5	Testicular Cancer N=2
Semen volume (ml)	3.4 ± 1.2	3.2 ± 1.2	3.2 ± 1.0	3.4
Sp. Concentration.	22.4 ± 11.2	28.8 ± 14.5	28.2 ± 18.2	30
Total Sp. Motility	48.2	46.5	44.2	46.4
Progressive Motility	32.4	36.2	38.4	38.2
Non- Motile	48.6	46.8	50.2	48.2
Abnormal morph	44.7	44.9	48.2	48.0
HOS (%)	44.2	44.8	42.8	42.4
Azoospermia	35 (40.2)*	3 (14.3)**	0 (0)	0 (0)

Versus ** p<0.05

HOS- Hypo-Osmotic Swelling Test

Sp.-Sperm

Morph –Morphology

Table 3: Comparison of Sperm Parameters between prepubertal and adult manifestation of Hernia.

Sperm Parameters	Pre pubertal Hernia N=26	Adult Hernia N=61	Pre pubertal Herniorrhaphy N=18	Adult Herniorrhaphy N= 69
Semen volume	3.2 ± 1.2	3.2 ± 1.2	3.4 ± 1.0	3.2 ± 1.0
Sp Concentration Million per ml	32.2 ± 12.2*	22.4 ± 8.6**	28.4 ± 14.2*	22.2 ± 10.2**
Total Sp. Motility	48.4*	38.6**	48.8*	40.2**
Non-motile Sp	38.6*	48.4**	36.8*	50.6**
Abnormal Morph	32.4*	38.4**	30.4*	40.4**
HOS (%)	48.4*	38.4**	46.8*	38.8**
Azoospermia (%)	5 (19.2)*	21 (34.4)**	4(19.1)*	22 (31.9)*

HOS-Hypo-Osmotic Swelling test

Versus ** p<0.05

Table 4: Hormone Profile.

LH (1U/L)	18 ± 8	10.9 -58.7
FSH(1U/L)	22 ± 4	16-114
Testosterone (nmol/L)	11.8 ± 3.8	10-40
Prolactin (mIU/L)	132 ± 45	72-511
Estrogen (pmol/L)	10.5 ± 40	73-324
FT4	14 ± 3.2	12-22

that follows the inguinal canal down into the scrotum, from around the 12th week of gestation. There has been paucity of research into association between inguinal hernia and male infertility. Since the Saccular Theory of hernia formation by Murray in 1907, there have been multiple theories of mechanisms of formation, which could be welded into a unified theory of Unified Theory of hernia formation. Collagen abnormality involving genetic and chromosomal abnormalities has been incriminated [32,33]. Not all cases of hypospadias neither qualified to be under the umbrella of TDS because infertility is not impaired and the role of environmental factors such as endocrine disrupting substances contributing to TDS have been addressed [28]. It is true that while there many studies have evaluated fertility after hernia repair and found it to be associated with male infertility mainly from testicular atrophy and low androgens, there are no studies evaluating fertility before hernia repair. However, we would like to speculate that hernia before repair may be associated with impaired sperm parameters. The mechanisms may include increased temperature and pressure on the testicular tissues, release of free radicals which result in oxidative stress and production and induction of oxidative stress and increased cadmium and low androgens in the intratesticular environment.

The constellation of male descent of testis, hypospadias, testicular

cancer and impaired spermatogenesis encompass the Testicular Dysgenesis Syndrome, This is in tacit agreement with Barker's hypothesis, in which the fetal environment has also been suggested to influence later health as an adult [34]. In a review, McMillen and Robinson [35] suggested critical windows during which perturbations of the intrauterine environment have major effects, and that epigenetic, structural, and functional adaptive responses result in a permanent fetal programming.

Future Research Direction

There is urgent to evaluate the association between hernia (before repair) and male fertility. If hernia causes male infertility, this will signpost the need to repair them early before complications that are life threatening or may cause testicular damages and compromise future male fertility set in. The factors that cause the persistent patency of the processus vaginalis, an embryonic developmental out-pouching of the peritoneal cavity that follows the inguinal canal down into the scrotum, from around the 12th week of gestation, should be aggressively explored

Conclusion

Genital disorders and corrective operation are associated with poor sperm parameters. Understanding of the mechanism of formation of hernia and whether or not it is part of the Testicular Dysgenesis Syndrome will enhance research into its origin and association with male infertility. In addition, this will result in the prevention and surgical management by well trained personnel.

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