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Epididymal Cysts: Are They Associated With Infertility?

David Weatherly, MD[1], Phil G. Wise, MD[2], Shawn Mendoca, MD[3], Aram Loeb, MD[1], Younjun Cheng, MS[4], John J. Chen, PhD[4], and George Steinhardt, MD[2]

Abstract

Scrotal sonography is commonly used for evaluation of the infertile male. While epididymal cysts are frequently observed during sonographic assessment, their presence has uncertain import. This study is a retrospective case-control sonographic and chart review comparison of infertile men and fertile volunteers to clarify the possible association of epididymal cysts and infertility. The study included 91 consecutively recruited patients from January 2012 to December 2014. The infertile group consisted patients with male factor infertility who underwent scrotal sonography (n = 67). The fertile group consisted of men requesting vasectomy who were recruited for study involvement and consented to undergo scrotal sonography (n = 24). The main outcome measure was infertility. The existence of epididymal cysts on scrotal sonography was the main risk factor. Predictably, the only sonographic findings associated with infertility were small testes (right: $t_{(df = 89)} = -2.52$; left: $t_{(df = 89)} = -2.28$, both $p = .01$) and the presence of a varicocele, $\chi^2_{(df = 1)} = 5.766$ with $p = .02$. The infertile men were also younger and more likely to use alcohol. Of the 91 men studied, 71% demonstrated epididymal cysts (73% of infertile and 67% of fertile men). Epididymal cysts were not be associated with infertility, $\chi^2_{(df = 1)} = 0.362$ with $p = .55$. This occurrence of epididymal cysts is the highest ever reported (71% of all men). While the occurrence of epididymal cysts in this cohort is unexplained, our observation that these cysts are not associated with infertility will be useful for those clinicians counseling patients observed to have these structures.

Keywords

epididymal cysts, infertility, scrotal sonography

Introduction

Scrotal sonography (SUS) is widely utilized for a wide variety of male conditions, including scrotal pain, scrotal masses, and infertility. Testicular size is best assessed with sonography and has obvious importance in assessing patients with fertility problems (Diamond et al., 2000). Testicular microlithiasis is appreciated only with SUS and, when associated with infertility, may have importance in terms of subsequent carcinogenesis (Elzinga-Tinke et al., 2010). Varicoceles present commonly as a scrotal mass and are also an identifiable cause of infertility, which is well assessed with this tool (Sakamoto, Ogawa, & Yoshida, 2008). Recent observations suggest an increase in sonographically determined epididymal cysts (ECs) at least in pediatric patients. A prior review of 2,200 pediatric scrotal ultrasounds showed an overall presence of EC in approximately 14%, with a higher incidence (35%) in boys older than age 15 years (Posey, Ahn, Junewick, Chen, & Steinhardt, 2010). Evaluations of asymptomatic adult men with SUS have revealed EC rates of 1.8% to 29% (Leung, Gooding, & Williams, 1984; Palmer et al., 2009). The medical consequences of EC are largely unknown as is the etiology. The only recognized cause of EC in humans relates to maternal ingestion of diethylstilbestrol (DES) which resulted in palpable EC in 20% of men so exposed in utero (Gill, Schumacher, Bibbo, Straus, & Schoenberg, 1979). This study was undertaken to investigate the possibility that EC may be related to infertility. Toward that end SUS was utilized to assess both fertile and infertile men to determine the sonographic and clinical features associated with infertility.

[1]Wayne State University School of Medicine, Detroit, MI, USA
[2]Urologic Consultants, Grand Rapids, MI, USA
[3]Michigan State College of Human Medicine, Grand Rapids, MI, USA
[4]University of Hawaii John A. Burns School of Medicine, Honolulu, HI, USA

Corresponding Author:
George Steinhardt, Urologic Consultants, 25 Michigan Street, NE Suite 3300, Grand Rapids, MI 49506, USA.
Email: gsteinhardt@urologic-consultants.com

Materials and Method

Institutional review board approval was obtained for this study (#2011-164). The charts of 67 consecutive men who presented to a male infertility specialist for evaluation of either primary or secondary male factor infertility were reviewed. Infertility was defined as the inability to father a child after a year of unprotected intercourse with a negative evaluation of the partner or a male found for whatever reason to have an abnormal semen analysis. As part of the infertility evaluation at the clinic, all infertile men underwent both SUS and semen analyses. Additionally, 24 men presenting for elective vasectomy were consented for study participation and then evaluated with SUS prior to their procedure. These men comprised the fertile group; all had reported paternity with a mean of 2.9 children per volunteer. A single experienced sonography technician using a 12MHZ probe performed SUS. EC were defined as sonolucent structures with measurable diameter (most often >3mm) located most often within the caput of the epididymis. Sonographic measurements recorded included testicular height, length, width, presence of ECs, and other scrotal pathology. Testicular volume was calculated by the Lambert equation ($L \times W \times H \times 0.71$; Lin, Huang, & Chen, 2009). The sonographic demonstration of both hydroceles and varicoceles was tabulated. Demographic and clinical variables were measured and summarized by descriptive statistics (mean, standard deviation, and range for continuous variable, such as weight, height, body mass index, age, and testicular volume; frequency and percentage for categorical variables, such as presence of ECs, varicoceles, and hydroceles). The status of alcohol use, tobacco use, and educational level were also summarized. Infertile and fertile patients were compared using two-sample two-tailed *t* tests for continuous variables and using chi-square or Fisher's exact tests for categorical variables. The associations between risk factors and infertility status were estimated using logistic regression analysis, with and without adjusting for covariates, for example, alcohol use, smoking history, age, body mass index, and average testicular volume. Odds ratios (*OR*s) and their 95% confidence intervals (95% CIs) were calculated. All analyses were performed in SAS 9.3 (SAS version 9.3. SAS Institute Inc.), and $p < .05$ was considered statistically significant.

Results

The comparison of clinical and demographic variables between the fertile and infertile groups is depicted in Table 1. Predictably, the infertile men had smaller testicular volumes (right: $t_{(df = 89)} = -2.52$; left: $t_{(df = 89)} = -2.28$, both with $p = .01$) and were more likely to demonstrate a varicocele, $\chi^2_{(df = 1)} = 5.766$, with $p = .02$, a common identifiable cause of infertility. The infertile men were also significantly younger, $t_{(df = 89)} = -2.97$ with $p = .01$, and more likely to relate alcohol use ($p = .03$, based on Fisher's exact test). The occurrence of EC by fertility status is depicted in Table 2. Of the 91 men included in this review, 65 (71%) had EC. Of these men with EC, 30% had bilateral cysts, 28% had left-sided cysts, and 12% had right-sided cysts. In the infertile population, 49 (73%) had EC. There was no statistical difference in the presence of EC, $\chi^2_{(df = 1)} = 0.362$ with $p = .55$, or the laterality of EC, $\chi^2_{(df = 2)} = 1.52$ with $p = .47$, comparing fertile and infertile men. The assessment of risk factors for infertility are demonstrated in Table 3 with only age (adjusted *OR* [95% CI]: 0.84 [0.75, 0.95]), testicular volume (adjusted *OR* [95% CI]: 0.86 [0.77, 0.96]), and varicocele (adjusted *OR* [95% CI]: 5.90 [1.52, 22.7]) suggesting associations with risk of infertility but not EC (unadjusted *OR* [95% CI]: 1.36 [0.50, 3.74], and adjusted *OR* [95% CI]: 2.27 [0.56, 9.15]). The only risk factor associated with the occurrence of EC was alcohol use (analysis not reported).

Discussion

There are no surprises in this study looking at infertility as an outcome for sonographic scrotal assessment. Predictably, younger age, alcohol use, smaller testicular size, and varicocele are all positively associated with the infertile status. Perhaps of more importance, it is reassuring that EC were not associated with infertility status in humans as may be true in experimental animals. Early rodent studies reported elevated rates of both infertility and genital abnormalities (including EC) in male rats exposed to DES in utero (McLachlan, Newbold, & Bullock, 1975). In addition to EC, adult men fetally exposed to DES demonstrate diminished sperm counts with poor sperm penetration assays when compared with controls (Whitehead & Leiter, 1981). While DES has been banned since the 1960s, there is great current concern that persistent organochloro compounds (POCs) act as endocrine disrupting estrogen mimetic agents with adverse consequences for male reproductive health (Skakkebaek, Rajpert-De Meyts, & Main, 2001). In humans, a few studies have looked at fetal estrogen exposure, Wolffian abnormalities, and human reproductive health. In 2009, Palmer et al. examined at a large cohort of men with fetal DES exposure. Clinically diagnosed EC were recalled in 4.6% of exposed men and 1.8% of non-exposed men, a difference that was felt to be significant; fertility was not assessed. Whitehead and Leiter (1981) reported not only an association between fetal DES exposure and EC but also infertility. Wilcox, Baird, Weinberg, Hornsby, and Herbst (1995) studied 548 men with known exposure to DES in utero and confirmed elevated rates of

Table 1. Comparison of Clinical and Demographic Variables Between Infertile and Fertile Groups.

	Infertile, n = 67; $M \pm SD$ (range)	Fertile, n = 24; $M \pm SD$ (range)	Test statistic value	p[a]
Age (year)	32.4 ± 5.2 (24-54)	36.2 ± 5.9 (30-54)	$t_{(df = 89)} = -2.97$	**.01**
Weight (lb)	204.6 ± 47.6 (154-415)	205.3 ± 37.0 (155-308)	$t_{(df = 88)} = -0.06$	.95
Height (in.)	71.1 ± 3.5 (60-77)	71.0 ± 2.6 (67-75)	$t_{(df = 88)} = 0.08$	.93
BMI	28.5 ± 6.3 (20.0-57.9)	28.5 ± 4.4 (23.6-41.8)	$t_{(df = 89)} = -0.05$	.96
Right testicular volume (cm^3)	18.3 ± 7.6 (2.5-37.4)	22.6 ± 5.6 (12.1-35.3)	$t_{(df = 89)} = -2.52$	**.01**
Left testicular volume (cm^3)	18.4 ± 7.7 (2.3-45.8)	22.3 ± 5.5 (11.0-32.1)	$t_{(df = 89)} = -2.28$	**.01**
	Infertile, n = 67; n (%)	Fertile, n = 24; n (%)		
Epididymal cysts			$\chi^2_{(df = 1)} = 0.362$	.55
No (n = 26)	18 (26.9)	8 (33.3)		
Yes (n = 65)	49 (73.1)	16 (66.7)		
Varicocele			$\chi^2_{(df = 1)} = 5.766$	**.02**
No (n = 38)	23 (34.3)	15 (62.5)		
Yes (n = 53)	44 (65.7)	9 (37.5)		
Hydrocele			$\chi^2_{(df = 1)} = 0.412$	.52
No (n = 58)	44 (65.7)	14 (58.3)		
Yes (n = 33)	23 (34.3)	10 (41.7)		
Smoker			NA	1.00
No (n = 73)	54 (80.6)	19 (82.6)		
Yes (n = 17)	13 (19.4)	4 (17.4)		
Alcohol use			NA	**.03**
No (n = 68)	46 (68.7)	22 (91.7)		
Yes (n = 23)	21 (31.3)	2 (8.3)		
Having college or higher degree			$\chi^2_{(df = 1)} = 0.019$	.89
No (n = 27)	20 (35.1)	7 (36.8)		
Yes (n = 49)	37 (64.9)	12 (63.2)		

Note. BMI = body mass index.
[a]p-values were based on two-sample two-tailed t tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. $p < 0.05$ was reported as statistically significant and indicated by bold font.

Table 2. Frequency Table of Epididymal Cysts Stratified by Fertility Groups.

	Infertile patients (n = 67)		Fertile patients (n = 24)		
	Frequency	Percentage	Frequency	Percentage	Test statistics value (p)[a]
Bilateral	23	34.33	5	20.83	$\chi^2_{(df = 2)} = 1.52$ (.47)
Unilateral	26	38.81	11	45.84	
Left	19	28.36	7	29.17	
Right	7	10.45	4	16.67	
None	18	26.87	8	33.33	

[a]Comparing epididymal cyst laterality (bilateral, unilateral, and none) versus fertility status (fertile and infertile).

genital abnormalities, especially when exposure occurred before the 11th week of gestation, but with no apparent effect on fertility.

While this current study also does not identify EC to be associated with infertility, the prevalence of EC is striking and exceeds all other previous reports. In 1999, Pierik, Dohle, van Muiswinkel, Vreeburg, and Weber evaluated 1,372 infertile men with scrotal ultrasound to assess anatomic abnormalities and reported a prevalence of sonographically determined ECs of 7.6%. Leung et al. (1984) utilizing SUS, evaluated 40 men without any known scrotal pathology by history or exam and identified ECs in 29%. More recently, Pezella et al. (2013) studied 75 infertile azospermic men in Italy with SUS and concluded there was no difference in the occurrence of EC comparing those with (22% with EC) to those without

Table 3. Assessment of Risk Factors for Infertility.

	Infertility	
	Unadjusted *OR* [95% CI]	Adjusted *OR* [95% CI]
Age (year)	0.89 [0.81, 0.97]**	0.84 [0.75, 0.95]***
BMI	1.00 [0.92, 1.08]	1.01 [0.90, 1.13]
Average testicular volume (cm^3)	0.91 [0.84, 0.98]**	0.86 [0.77, 0.96]**
Smoker (yes vs. no)	1.14 [0.33, 3.94]	3.26 [0.48, 22.15]
Alcohol use (yes vs. no)	5.02 [1.08, 23.4]*	2.53 [0.38, 16.66]
Epididymal cysts (yes vs. no)	1.36 [0.50, 3.72]	2.27 [0.56, 9.15]
Varicocele (yes vs. no)	3.19 [1.21, 8.40]*	5.90 [1.53, 22.7]**
Hydrocele (yes vs. no)	0.73 [0.28, 1.90]	0.69 [0.19, 2.44]

Note. *OR* = odds ratio; CI = confidence interval; BMI = body mass index.
*$p < .05$. **$p < .01$. ***$p < .001$.

(12% with EC) obstructive azospermia. The experience with pediatric EC suggested a rising prevalence of cysts in older patients approaching 35% in boys older than 15 years of age (Posey et al., 2010). In this current study, EC occurred in 67% of fertile compared with 73% of infertile men, not a significant difference. As previously noted, fetal DES exposure does not explain the high occurrence of ECs seen in both the adult and pediatric populations as this medication was banned long ago. There is much interest in a wide variety of man-made POCs that can stimulate the estrogen receptor fetally or postnatally with the potential for demonstrable effects on male reproductive health including EC (Skakkebaek et al., 2001). As both the current and prior pediatric studies were done in Grand Rapids, Michigan, it is plausible to consider an environmental explanation for the unprecedented occurrence of EC. Michigan is surrounded by the Great Lakes and is notably home to many chemical companies. Throughout Michigan, there has been great concern about the baseline contamination with polychlorinated biphenyls manufactured locally in the past. The entire state was contaminated in the early 1970s when the flame retardant polychlorinated biphenyl was inadvertently introduced into cattle feed and hence the food chain in the state. It is worthwhile to note that polybrominated diphenyl ether (another flame retardant) levels are highest in bald eagle populations in Michigan compared with elsewhere in Canada and the United States (Dornbos et al., 2015). Given these observations, it is possible that men in Michigan are more at risk for exposure to POCs because of geographic constraints and environmental contamination. In any event, the observed rate (71%) of EC is more than twice what has previously been reported in adults. While the study cannot comment on the etiology of this finding, environmental influences are a possibility.

The current study is retrospective in design and, therefore, inherently limited by selection bias. Additionally, the relatively small number of fertile (vasectomy) subjects recruited is a limitation of this work. It is conceivable that larger recruitment of fertile males may have disclosed an association of EC with infertility. As another limitation, the fertile men were not evaluated with a semen analysis and fertility status was supported only by a history of paternity. Among infertile patients, semen abnormalities (e.g., motility, morphology, and concentration) do not seem to be associated with the existence of EC (results not shown). Last, some might argue that the high prevalence of EC in the study groups was because of the precision of modern sonographic equipment. It is true that the machines are much better now than in the past, but EC determination does not require sophisticated equipment as the structures are easily demonstrated to be sonolucent with strong back walls and enhanced through transmission. These features are well demonstrated with even the earliest sonographic instruments.

Conclusions

ECs are a very common finding on adult scrotal ultrasounds with a rate approximately double that seen in the teenage pediatric population. Though the reason for the high prevalence of EC is unknown, there is no evidence to suggest that the presence of these cysts is associated with infertility. This information will be useful in counseling patients incidentally diagnosed to have EC on sonographic assessment performed for a wide variety of clinical problems.

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Authors' Note

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