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## INVITED REVIEW

# Varicocele and testicular function

Male Fertility

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Testicular varicocele, a dilation of the veins of the pampiniform plexus thought to increase testicular temperature via venous congestion, is commonly associated with male infertility. Significant study has clarified the negative impact of varicocele on semen parameters and more recent work has shed light on its detrimental effects on the molecular and ultrastructural features of sperm and the testicular microenvironment, as well as more clearly defined the positive impacts of treatment on couples' fertility. The relationship between varicocele and testicular endocrine function, while known for some time based on histologic evaluation, has become more apparent in the clinical setting with a growing link between varicocele and hypogonadism. Finally, in the pediatric setting, while future study will clarify the impact of varicocele on fertility and testicular function, recent work supports a parallel effect of varicocele in adolescents and adults, suggesting a re-evaluation of current treatment approaches in light of the progressive nature of the condition and potential increased risk of future disease.

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### INTRODUCTION

Testicular varicocele is a dilation of the veins of the pampiniform plexus draining the testicle. Varicoceles are found in 15% of all men and in 19%–41% of men who present with primary infertility, representing the most common surgically treatable cause of male infertility.<sup>1</sup> In men with secondary infertility, varicoceles are an underlying cause in 45%–81% of patients, and varicocele remains the most common cause of male infertility worldwide.<sup>1–3</sup> In men with azoospermia, the incidence of varicocele is 4.3%–13.3%.<sup>4</sup> Based on a 15% prevalence of infertility in the population, approximately 20% of men with varicocele have evidence of infertility, while 80% do not.<sup>5</sup> While varicocele can be associated with testicular discomfort and atrophy, the negative effects of varicocele on male fertility and semen parameters, as well as recent evidence identifying varicocele as a risk factor for hypogonadism, are the most relevant ramifications of the condition.<sup>6,7</sup>

In this review, we summarize the most recent literature linking varicocele to male infertility and hypogonadism. Given the progressive nature of the effects of varicocele on sperm production and function, as well as Leydig cell function over time, we also discuss the approach to varicocele in pediatric and adolescent populations, with emphasis on consideration of downstream ramifications of untreated varicocele in these young males.

### VARICOCELE PATHOPHYSIOLOGY

While left-sided varicoceles predominate, a contralateral varicocele is present in 30%–80% of cases.<sup>8</sup> In contrast, isolated right-sided varicoceles comprise <5% of cases and should raise concern for a retroperitoneal mass effect.<sup>9</sup> The high incidence of varicocele in humans may be in part explained by our upright posture, resulting in venous congestion.<sup>10</sup> Several other anatomic explanations for the

more common incidence of left-sided varicoceles also exist. First, venous valves are more commonly absent on the left-side, with one study finding valves absent in 40% of left spermatic veins, but absent in only 23% of right spermatic veins.<sup>11</sup> However, 26% of patients with varicocele have competent valves, making the absence of valves an unlikely unifying cause of varicocele.<sup>12</sup> Second, right-sided testicular venous drainage is directly into the inferior vena cava, whereas the left spermatic vein drains into the left renal vein, which drains more slowly than the vena cava due to its smaller diameter. Several case studies in men with *situs inversus* and right-sided varicocele, as well as venographic studies in men with right-sided varicocele and spermatic vein drainage into the right renal vein, support slower spermatic venous drainage on the side draining into a renal vein.<sup>13–16</sup> Third, left-sided spermatic vein drainage increases the chances of renal vein compression between the superior mesenteric artery and aorta or obstruction of the left common iliac vein by the left common iliac artery as it crosses above the vein.<sup>17</sup> However, this type of compression occurs in only 0.5%–0.7% of cases, making this phenomenon a rare cause of varicocele.<sup>12</sup> Interestingly, predisposition to varicocele likely has a genetic component, with one study demonstrating varicocele in 56.5% of first-degree relatives of patients with varicoceles, in contrast with 6.8% of controls.<sup>18</sup> However, predisposing genes remain to be identified.

The prevailing theory explaining impairments in testicular function resulting from varicocele posits that poor venous drainage increases testicular temperature, leading to detrimental effects on spermatogenesis and Leydig cell function. Normal scrotal temperature is 1–2°C lower than body temperature, and is maintained by the thin scrotal skin, a lack of subcutaneous fat, and a countercurrent heat

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exchange system taking advantage of the pampiniform plexus, allowing arterial blood to be cooled as it enters the testis.<sup>19</sup> Higher intratesticular temperatures have been reported in men with varicocele and fertility difficulties,<sup>20,21</sup> and numerous animal and human studies have linked scrotal and testicular hyperthermia to decrements in spermatogenic function, including in the setting of cryptorchidism.<sup>22–26</sup>

Other theories to explain the testicular effects of varicocele include: (1) suboptimal drainage of testicular gonadotoxins due to venous dilatation, (2) reflux of renal and adrenal metabolites contributing to venous dilatation, (3) testicular hypoxia, (4) higher levels of oxidants in the semen, and (5) anti-sperm antibodies.<sup>27–33</sup> On a cellular and molecular level, varicocele has been shown to decrease testicular DNA polymerase activity, increase testicular cell apoptosis, increase reactive oxygen species (ROS), alter Sertoli cell function, and decrease Leydig cell testosterone secretion.<sup>32,34–36</sup> While all of the above-mentioned varicocele causes have some evidentiary support, no one cause describes all cases of varicocele, and multiple etiologies may contribute to any single case. In addition, identifying the root causes of varicocele in all patients may not be economically viable and is unlikely to have a significant impact on outcomes if the varicocele is treated using current modalities. Nevertheless, it is helpful to conceptualize the origins of varicoceles in consideration of future treatments that may obviate the need for surgical intervention and specifically address the root cause of the varicocele.

### TESTICULAR EFFECTS OF VARICOCELE

Historically, varicocelectomy did not become part of the armamentarium for managing infertile men until the 1950s, when Tulloch demonstrated improvement in semen parameters in 26 of 30 patients after varicocelectomy, with 10 men having return of normal semen parameters and initiating pregnancy.<sup>37</sup> In a 1977 study evaluating testicular size in a group of 82 healthy volunteers, 61 subfertile men with varicocele, and 27 subfertile men without varicoceles, Lipshultz and Corriere observed testicular atrophy preferentially on the ipsilateral side in men with varicocele, although no differences in semen parameters were observed between groups.<sup>38</sup> This initial link between testicular atrophy and varicocele was further supported by Johnsen and Agger, who evaluated testicular biopsies before and one year after varicocele repair in 29 men, finding significant improvements in the appearance of seminiferous tubules after surgery and linking varicocele with germ cell content.<sup>39</sup>

#### Cellular effects on sperm

The effects of varicocele on semen parameters were first made apparent by MacLeod in 1965, when he noted a decrease in sperm motility and density.<sup>29</sup> In addition, a “stress pattern” of morphologic changes, not specific to varicocele but including increased numbers of immature forms, amorphous cells, and tapered forms, was also observed. Abnormal sperm morphology in men with varicocele has been repeatedly observed, but to date, no morphologic changes specific to varicocele have been identified.<sup>40–42</sup> Even with the use of Kruger strict morphologic criteria, only a decrease in the number of normal forms has been observed in men with varicocele, with improvements in morphologic criteria after varicocele repair.<sup>43,44</sup> Functionally, sperm from men with varicocele are less able to fuse with female gametes. These sperm bind to hamster and human oocytes, and penetrate hamster oocytes, less well than sperm from normal men.<sup>45,46</sup>

#### Reactive oxygen species and DNA damage

On a molecular level, men with varicocele have significantly higher levels of ROS, which can be present together with higher levels of

DNA fragmentation, corresponding to damage of packaged chromatin and a reflection of poor sperm quality.<sup>32,47</sup> While the mechanisms of ROS action have been incompletely elucidated, studies suggest that oxidation and reduction are important in sperm hyperactivation, capacitation, zona pellucida binding, and the acrosome reaction.<sup>48,49</sup> Varicocele is associated with increased DNA damage, and exposure to sperm to exogenous ROS can induce DNA damage, particularly in the absence of appropriate antioxidant mechanisms.<sup>50,51</sup> ROS are elevated both in the semen as well as systemically in men with varicocele, and varicocelectomy results in a decrease in ROS, improvement in antioxidant levels, and decreases in DNA damage.<sup>32,52–55</sup> In uncontrolled studies of men with impaired semen parameters with and without varicocele, dietary antioxidant therapy results in improvement in semen parameters, including sperm concentration and motility, even when men with varicocele do not undergo varicocelectomy.<sup>56–59</sup> Thus, while varicocele predisposes to oxidative damage and compromised DNA integrity, varicocele treatment using medical and surgical approaches can reverse these molecular changes.

#### Ultrastructural changes in sperm in men with varicocele

The use of the current semen parameters in the evaluation of male infertility is suboptimal, given that sperm count, morphology determined using light microscopy, forward progression, and motility are largely nonspecific indicators of fertility and incompletely reflect sperm quality and function. In the setting of varicocele, changes in semen parameters after varicocele repair are inconsistent across the literature, with many studies reporting improvements in one or more parameters, but some reporting no changes.<sup>60–63</sup> Meta-analyses evaluating the effects of varicocelectomy show improvements in semen parameters overall, but evaluation of sperm and seminiferous tubule histology and ultrastructure in the setting of varicocele before and after treatment may better inform the effects of treatment, particularly in consideration of a growing proportion of infertile couples utilizing assisted reproductive technologies (ART).

A 1978 study evaluating sperm histology in the setting of varicocele observed multinuclear spermatids, suggesting a disturbance in spermiogenesis.<sup>64</sup> A follow-up study in 1980 evaluated testicular biopsies from 21 men with varicocele using light and electron microscopy, demonstrating spermatid malorientation relative to Sertoli cells and structurally abnormal Sertoli-germ cell junctional complexes, highlighting an adluminal compartment defect in varicocele and suggesting that the Sertoli cell is more sensitive to varicocele pathology than sperm.<sup>65</sup> Subsequent ultrastructural studies demonstrated increased vacuolization of the endoplasmic reticulum, with possible resultant exfoliation of germ cells and abnormal retention of cytoplasmic droplets.<sup>66,67</sup> In a study of quantitative ultramorphological analysis, Reichart *et al.* examined sperm subcellular organelles in men with treated and untreated varicoceles, finding a significant increase in normal acrosome structure, chromatin condensation, and sperm head appearance, but observing no changes in tail subcellular organelles, in men with treated varicoceles.<sup>68</sup> In contrast, no changes in semen parameters were observed between groups. This work implicated alterations in sperm head formation and DNA packaging in varicocele pathogenesis and highlighted ultramorphology as a more sensitive tool for assessment of the sperm pathology in the setting of varicocele.

Sperm derived from men with varicocele are also more likely to retain cytoplasmic droplets, which are correlated with ROS production and DNA damage, defective sperm function, impaired spermatogenesis, and worse *in vitro* fertilization rates, more frequently than sperm from fertile men.<sup>66,69–71</sup> When assessing the relationship

between varicocele and sperm function relating to sperm tailpiece mitochondrial activity, Blumer *et al.* found a higher percentage of men with varicocele to have inactive mitochondria, demonstrating a functional tailpiece defect not previously observed using ultrastructural evaluation.<sup>72</sup> Importantly, varicocele repair results in improvement in sperm ultrastructure, namely sperm head organelle defects, according to a recent meta-analysis of prospective studies.<sup>73</sup>

**Sertoli and Leydig cell function and hypogonadism**

In addition to direct effects on sperm, varicoceles have a detrimental impact on other testicular cell types as well. Clinically, Sertoli cell dysfunction can be observed by a decreased responsiveness to follicle stimulating hormone (FSH), and by alterations in androgen binding protein (ABP), transferrin, and inhibin. In the setting of varicocele, some men present with elevated FSH and decreased testosterone production, and 48%–76% have improvement in one or both of these parameters following varicocelectomy.<sup>74,75</sup> Inhibin B levels also often improve after varicocelectomy, suggesting a reversible Sertoli cell defect.<sup>76</sup> In animal models of varicocele, Sertoli cell dysfunction may also be observed through decreased ABP and transferrin levels, both of which can disrupt spermatogenesis.<sup>77</sup> In human studies, varicocelectomy results in a rise in transferrin levels, correlating with increased sperm concentration and with improvements in sperm morphology.<sup>78</sup> Ultrastructurally, seminiferous tubules from men with varicocele demonstrate thickening of the germinal epithelium with increased apoptosis, Sertoli and germ cell cytoplasmic vacuolization, and alterations in spermatids and spermatozoa.<sup>79</sup>

The impact of varicocele on Leydig cell structure has also been studied. Sirvent *et al.* observing increased cytoplasmic vacuolization and atrophy in Leydig cells, and a decrease in the number of Leydig cells, even in bilateral testes in men with unilateral varicocele.<sup>80</sup> Leydig cell malfunction may predispose men to clinical hypogonadism. Studies evaluating serum testosterone levels in men with varicocele have yielded

variable results, with some early studies finding decreased levels<sup>81,82</sup> and others showing no difference.<sup>83,84</sup> A large study by the World Health Organization in 1992 reported on 9034 men presenting for fertility evaluation and observed that men with varicocele over age 30 had significantly lower testosterone levels than men <30 years old with varicocele,<sup>85</sup> a trend not observed in men without varicocele suggesting an impact on Leydig cell function. Several studies evaluating the effects of varicocele repair have reported normalization of serum testosterone levels after repair, indicating a reversible effect<sup>75,86–88</sup> (Table 1).

More recent studies more clearly support a detrimental impact of varicocele on testosterone levels, with a 2007 study by Tanrikut *et al.* showing a significantly lower serum testosterone level in men with varicocele (412.2 ng dl<sup>-1</sup>) than in men without (462.6 ng dl<sup>-1</sup>).<sup>89</sup> A follow-up study by the same group in 2011 showed a significant increase (178 ng dl<sup>-1</sup>) in serum testosterone levels after varicocele repair irrespective of varicocele grade, laterality or patient age, more strongly implicating varicocele as a risk factor for androgen deficiency or hypogonadism.<sup>7</sup> Other recent studies have also echoed these results.<sup>90–92</sup> Improvement in testosterone levels appears to be age-independent, with one study of 272 men aged 16–65 years old who underwent varicocelectomy demonstrating similar improvements in both semen parameters and testosterone levels independent of age.<sup>93</sup> To further strengthen the link between varicocele and hypogonadism, a recent query of the Truven Health Analytics MarketScan database, a large outpatient claims database, demonstrated an increased number of hypogonadism claims in young men who had concurrent varicocele claims among more than 224 000 men.<sup>94</sup>

Several studies have evaluated the relationship between varicocelectomy and hypogonadal symptoms, namely erectile dysfunction (ED), finding improvement in erectile function in men undergoing varicocelectomy. In a 2011 study of 200 hypogonadal infertile men with varicocele treated using varicocelectomy or ART, both significant increase in serum testosterone, with 78% of patients

**Table 1: Effects of varicocele repair on serum testosterone levels**

Paper	Year published	Number of patients with varicocele	Varicocele treatment	Baseline testosterone (ng dl <sup>-1</sup> ) (mean [s.d.]) <sup>a</sup>	Postvaricocelectomy testosterone (ng dl <sup>-1</sup> ) (mean [s.d.]) <sup>a</sup>	P
Su <i>et al.</i> <sup>86</sup>	1995	35	Microsurgical	319±12	409±23	0.0004
Cayan <i>et al.</i> <sup>75</sup>	1999	78	Microsurgical	563±140	837±220	<0.01
Fujisawa <i>et al.</i> <sup>76</sup>	2001	52	Microsurgical	460±160	470±190	NA
Gat <i>et al.</i> <sup>87</sup>	2004	83	Embolization	348±175	496±243	<0.001
Lee <i>et al.</i> <sup>151</sup>	2007	18	Microsurgical	360±191	416±358	0.25
Di Bisceglie <i>et al.</i> <sup>91</sup>	2007	38	Sclerotherapy	650±50	660±50	0.97
Hurtado de Catalfo <i>et al.</i> <sup>88</sup>	2007	36	Not specified	298±17	398±20	NA
Rodriguez Peña <i>et al.</i> <sup>152</sup>	2009	202	Not specified	648±156	709±232	>0.05
Tanrikut <i>et al.</i> <sup>7</sup>	2011	325	Microsurgical	358±126	454±168	<0.001
Sathya Srini and Belur Veerachari <sup>95</sup>	2011	100	Microsurgical	177±18	301±43	<0.001
Zohdy <i>et al.</i> <sup>96</sup>	2011	103	Microsurgical	379±206	450±170	<0.001
Hsiao <i>et al.</i> <sup>93</sup>	2011		Microsurgical			
Age<30 years		52		418±21	511±25	NA <sup>b</sup>
Age 30–39 years		144		422±13	481±25	NA
Age 40+ years		66		401±19	474±32	NA
Hsiao <i>et al.</i> <sup>90</sup>	2013	59	Microsurgical	308±7	418±15	<0.0001
Abdel-Meguid <i>et al.</i> <sup>92</sup>	2014		Microsurgical			
Varicocele infertile treatment		66		347±132	399±99	<0.0001
Varicocele infertile control		33		340±126	350±126 <sup>c</sup>	0.07
Varicocele fertile control		33		397±165	392±154 <sup>c</sup>	0.56
Normal control		33		505±150	NA	

<sup>a</sup>Serum testosterone values reported in units other than ng dL<sup>-1</sup> have been converted to facilitate comparisons; <sup>b</sup>Results for each age group reported as significant in the cited paper, but P values were not provided; <sup>c</sup>This group did not receive varicocelectomy. s.d.: standard deviation; NA: data not available



becoming eugonadal, as well as decrease in ED prevalence were observed in the varicocelectomy group.<sup>95</sup> In contrast, no change in testosterone levels, and a slight increase in ED prevalence were observed in the ART group. In a similar study, 141 hypogonadal infertile men with clinical varicocele were treated using varicocelectomy or ART, also with normalization of testosterone levels in 76% of men. International Index of Erectile Function-5 questionnaire scores in men undergoing varicocelectomy also increased in this study, suggesting improvement in sexual function.<sup>96</sup> While serum testosterone levels are most frequently used to assess Leydig cell function, intratesticular testosterone levels are a key factor in the regulation of spermatogenesis. Although no studies of intratesticular testosterone relating to varicocele in humans exist, a recent rat model demonstrated a significant decrease in intratesticular testosterone levels in the setting of varicocele, suggesting a direct impact on Leydig cell function using a more rigorous and sensitive metric.<sup>97</sup>

Thus, while definitive data linking varicocele to hypogonadism remain elusive, with large prospective studies, as well as studies evaluating the long-term maintenance of eugonadism in men with a history of varicocele lacking, the link between testicular endocrine function and varicocele is growing stronger and should be considered, particularly in the evaluation and treatment of young men with varicocele.

**VARICOCELE AND MALE FERTILITY**

As described above, semen parameters, as well as the seminal and testicular milieu and ultrastructure may be impacted by varicocele, with varicocele being implicated as a causal factor in many infertile males. While treatment of varicocele is not appropriate or necessary in all cases, an improved understanding of ultrastructural changes and improvement following varicocelectomy may argue for varicocele treatment in most men.

**MEN WITH CLINICAL VARICOCELE**

Numerous studies, including several randomized controlled trials (RCTs) support a benefit to semen parameters in infertile or subfertile men undergoing varicocelectomy, providing high-level evidence in favor of treatment (Table 2). In addition to individual studies, meta-analyses evaluating both prospective and randomized studies have also indicated a favorable effect of varicocelectomy on semen parameters.<sup>1,98</sup> A recent meta-analysis quantified the improvement in several semen parameters, finding an increase in sperm density of 12.32 million sperm per ml and in motility of 10.36%,

and found that varicocelectomy improves seminal oxidative stress, sperm DNA damage, and sperm ultramorphology.<sup>73</sup> These latter factors are of particular significance when discussing treatment in couples considering ART, and will be discussed in more detail below. Varicocele grade also impacts semen parameters, with higher-grade varicoceles having a more significant impact. Correspondingly greater improvements in semen parameters are observed in men with higher-grade (2 or 3) varicoceles after repair.<sup>99</sup> The effects of varicocele on semen parameters appear to be age-independent, with men ages 14 to >40 years old having similar semen parameters in the setting of varicocele.<sup>100</sup>

While many studies have evaluated the effects of varicocelectomy on semen parameters, fewer have addressed the impact on pregnancy rates. Several RCTs have demonstrated improvement in clinical pregnancy as a result of varicocelectomy (Table 2), and a 2007 meta-analysis of five studies found an odds ratio of 2.87 in favor of varicocele with respect to spontaneous pregnancy in men with clinical varicocele and at least one abnormal semen parameter treated with surgical varicocelectomy, with a number needed to treat of 5.7.<sup>101</sup>

Men with isolated sperm defects and clinical varicocele may also benefit from treatment according to a 2008 study by Boman *et al.* evaluating 118 infertile men with clinical varicocele and isolated asthenospermia.<sup>102</sup> In this study of 69 men undergoing varicocelectomy and 49 who were observed, varicocelectomy resulted in increases in total motile sperm count and pregnancy rate (65% vs 32% in the observation group). Men with varicocele who are in relationships with recurrent pregnancy loss may also benefit from repair. The results of a 2012 clinical trial comparing varicocelectomy to observation in men whose partners had recurrent first trimester pregnancy loss showed significant improvements in semen parameters, higher spontaneous pregnancy rates (44% vs 19%), and lower miscarriage rates (19% vs 69%).<sup>103</sup> While the authors did not assess chromatin integrity in their cohort, these results argue that varicocelectomy serves to decrease the risk of transmission of genetic defects that may arise in the setting of increased DNA damage due to varicocele. It is important to mention, however, that men in relationships experiencing recurrent pregnancy loss may carry genetic defects, and that these can be diagnosed in some cases using sperm fluorescence *in situ* hybridization or another genetic testing.<sup>104</sup> To better determine the optimal time frames for treatment response, a recent study by Al Bakri *et al.* established that semen parameters improve significantly up to 3 months after varicocelectomy, with little

**Table 2: Effects of varicocele repair on semen parameters and pregnancy rates in men with clinical and subclinical varicocele in randomized controlled studies**

Paper	Year published	Number of varicocele cases	Mean male age (years)	Improved semen parameters	Higher clinical pregnancy rate	P*
Clinical varicocele						
Nilsson <i>et al.</i> <sup>153</sup>	1979	96	NA	No	No	NA
Madgar <i>et al.</i> <sup>154</sup>	1995	45	29	Yes	Yes	0.001
Nieschlag <i>et al.</i> <sup>155</sup>	1998	125	33	Yes	No	NS
Krause <i>et al.</i> <sup>156</sup>	2002	67	32	No	No	0.18
Al-Kandari <i>et al.</i> <sup>157</sup>	2007	147	30	Yes	No	NS
Abdel-Meguid <i>et al.</i> <sup>158</sup>	2011	145	29	Yes	Yes	0.01
Mansour Ghanaie <i>et al.</i> <sup>103</sup>	2012	68	36	Yes	Yes	0.003
Subclinical varicocele						
Yamamoto <i>et al.</i> <sup>110</sup>	1996	85	32	Yes	No	0.76
Grasso <i>et al.</i> <sup>111</sup>	2000	68	NA	No	No	NS
Unal <i>et al.</i> <sup>112</sup>	2001	42	33	Yes	No	0.59

\*P value related to pregnancy rate. NA: data not available; NS: nonsignificant





further improvement thereafter.<sup>105</sup> This rapid timeline to realizing the benefits of varicocele repair is important and argues for varicocele correction even in couples with advanced maternal age, where timing is critical. Thus, currently available evidence argues for varicocele repair in most men with clinical varicocele and impaired semen parameters, with demonstrated benefits regarding spontaneous pregnancy rates, arguably the most important outcome of male fertility treatment.

### MEN WITH SUBCLINICAL VARICOCELE

While the benefits of varicocelectomy in men with clinical varicocele are clear, the approach to men with subclinical varicocele, defined as a varicocele not palpable on physical exam and identified only using Doppler ultrasonography using a venous diameter of  $\geq 3$  mm and reversal of flow, is less obvious. However, up to 50% of infertile men without clinical varicocele may have subclinical varicocele, suggesting that subclinical varicocele contributes to infertility.<sup>106</sup> In addition, men with unilateral clinical varicocele may also have a subclinical contralateral varicocele 25% of the time.<sup>107</sup> Several studies, including RCTs, have observed improvement in semen parameters without an impact on pregnancy rates in men with subclinical varicocele<sup>106,108–112</sup> (Table 2). A 1995 study comparing improvements in semen parameters and pregnancy rates after varicocelectomy in 40 infertile men with clinical varicocele and 46 infertile men with subclinical varicocele showed significant improvements in semen parameters in both groups after treatment, and no difference in clinical pregnancy rates between men with clinical and subclinical varicocele, arguing for repair in all infertile men with any type of varicocele.<sup>60</sup> A larger recent study evaluating semen parameters and pregnancy rates in 143 men with subclinical left-sided varicocele undergoing microsurgical varicocelectomy, medical treatment with *L*-carnitine, or observation demonstrated improvement in semen parameters and a higher pregnancy rate in both the *L*-carnitine and surgically treated groups, with surgery having the highest (60%) pregnancy rate relative to observation (19%).<sup>113</sup> Similarly, in a study of 42 men with subclinical varicocele randomized to varicocelectomy or clomiphene citrate therapy, more significant improvements in semen parameters were observed in the varicocelectomy group, and while there was no significant difference in pregnancy rates between groups, the varicocelectomy group reported a 12.5% pregnancy rate, whereas the medical therapy group's pregnancy rate was 6.7% ( $P = 0.59$ ).<sup>112</sup> Many of the above studies have been underpowered, likely accounting at least in part for the inconsistent effects observed on pregnancy rates. As such, more work is needed to evaluate the efficacy of subclinical varicocele repair on both semen parameters as well as pregnancy rates before conclusions regarding outcomes and treatment recommendations can be made.

### VARICOCELE AND ASSISTED REPRODUCTIVE TECHNOLOGIES

In men with spermatogenic failure, the use of ART may be unavoidable. However, men with nonobstructive azoospermia (NOA) and clinical varicocele represent a subset of infertile men with spermatogenic failure in whom varicocelectomy may obviate the need for ART or lessen the degree of ART needed to initiate a pregnancy. In the context of men with NOA, varicocelectomy success is defined as the presence of sperm in the ejaculate and has been variable across studies. The recent, uncontrolled retrospective literature evaluating a total of 262 patients reports the presence of any sperm in the ejaculates of 21%–56% of men postvaricocelectomy, with a maximum sperm concentration of 3.8 million  $\text{ml}^{-1}$ .<sup>114,115</sup> However, between 5% and 35% of NOA men will occasionally have sperm in the ejaculate without treatment, with relapse

of azoospermia in approximately 25%.<sup>116–119</sup> Kim *et al.* evaluated 28 men with a history of azoospermia with uni- or bilateral-varicocele, finding return of sperm in the ejaculate of 43% of men after varicocelectomy.<sup>120</sup> The likelihood of finding sperm in the ejaculate was directly related to testicular histology, with men with hypospermatogenesis or late maturation arrest having sperm, and men with early maturation arrest or Sertoli cell only histology having none. In this study, all couples eventually required ART to initiate pregnancy. A subsequent meta-analysis by Weedin *et al.* evaluating 11 studies encompassing 233 patients with NOA found motile sperm in the ejaculates of 91 (39.1%) patients after varicocelectomy with 14 (6%) spontaneous pregnancies being reported.<sup>121</sup> Again, the likelihood of sperm in the ejaculate was influenced by prerepair testicular histology, with the highest likelihood of sperm in men with hypospermatogenesis (55%) or late maturation arrest (46%), in contrast with men with early maturation arrest (0%) or Sertoli cell only (11.3%). In a 2012 study evaluating factors predicting recovery of spermatogenesis in 31 men with NOA and varicocele, testicular histology impacted the likelihood of sperm in the ejaculate, and while 32% of men had sperm in their ejaculates postvaricocelectomy, persistent recovery was found in only 19%, intermittent recovery in 6.5%, and relapse of azoospermia in 6.5%.<sup>122</sup> When considering viable sperm obtained after varicocelectomy in NOA men, one study found that of the 22% of NOA men who developed sperm in the ejaculate after varicocelectomy, <10% had viable sperm for intracytoplasmic sperm injection (ICSI), therefore requiring testicular sperm extraction (TESE).<sup>117</sup> When undergoing microsurgical TESE, however, there was no difference in sperm retrieval rates between men with NOA with and without varicocele. In contrast, others have found that varicocele repair does increase sperm retrieval rates in men with NOA undergoing ICSI.<sup>123,124</sup>

In couples undergoing ART, the decision to repair a varicocele should take into consideration each couple's individual set of circumstances. In the setting of female factor infertility alone, varicocele repair is not recommended.<sup>9</sup> In couples with both male and female factor contributions, varicocelectomy may facilitate ART, independent of female partner age, with sperm being obtained from the ejaculate rather than requiring a testicular biopsy specimen.<sup>125</sup> As described above, in some men with azoospermia, varicocele repair may result in sperm in the ejaculate, obviating the need for TESE. However, recent work showed higher pregnancy rates in couples using testicular rather than ejaculated sperm, albeit in cryptozoospermic men, suggesting that a steadfast desire to use ejaculated sperm may be unwarranted.<sup>126</sup> Nevertheless, initially azoospermic men should be counseled that ART will likely be necessary to produce a pregnancy, as natural conception is relatively rare in these cases.

The molecular milieu of the sperm and egg should be given particular consideration in the setting of ART, which bypasses normal mechanisms for preventing transmission of genetic defects. Elevated levels of sperm DNA damage may impact pregnancy rates, with a recent meta-analysis demonstrating a higher likelihood of pregnancy in couples using ART when the DNA fragmentation index was in the normal range.<sup>127</sup> Earlier studies had observed variable relationships between sperm DNA integrity testing and pregnancy rates using ART, and some had observed an increased risk of spontaneous abortion when using sperm with higher levels of DNA damage.<sup>128–130</sup> Importantly, elevated levels of sperm DNA damage correlate with numerical chromosomal abnormalities, which increase the risk of birth defects in couples using ART.<sup>131,132</sup> Varicocele repair improves oxidative and DNA damage and sperm ultramorphology, and offers a medication-free path to higher quality sperm.

In couples using ART, the benefit of varicocelectomy on pregnancy rate remains incompletely defined, although appears to overall show a benefit. In a 2012 retrospective review evaluating 248 couples undergoing ICSI, the 169 couples in which men had undergone varicocele repair prior to ICSI did not have higher pregnancy, implantation, or miscarriage rates than the 79 couples in whom varicocele was not repaired.<sup>133</sup> In contrast, other studies have demonstrated improvement in pregnancy rates in couples using ART after varicocele repair. In one study evaluating the impact of varicocelectomy on ICSI outcomes in 242 men with clinical varicocele, an increase in the number of motile sperm and a decrease in the sperm defect score was observed in men after varicocelectomy, with higher pregnancy and live birth rates in the treated group, indicating improved sperm quality in men with treated varicocele.<sup>134</sup> Similarly, a study evaluating 58 couples undergoing intrauterine insemination with the men having a history of varicocele found higher pregnancy and live birth rates in couples in which the varicoceles had been treated, despite no differences in postwash sperm counts, also supporting improvement in sperm characteristics not evaluated using current semen parameters.<sup>135</sup> Thus, varicocelectomy is likely to improve molecular features of sperm not routinely considered during contemporary infertility evaluation and treatment, but nonetheless essential for optimal outcomes.

When considering the comprehensive landscape of fertility treatment, varicocele repair may offer a permanent solution to male factor infertility or may shift the level of ART necessary to achieve pregnancy down.<sup>136</sup> In addition, varicocelectomy is significantly more cost effective than ICSI, with the cost per delivery after varicocelectomy estimated at \$26 268, in comparison with \$89 091 for ICSI, and with no difference in efficacy rates per pregnancy between the two approaches.<sup>137</sup>

#### ADOLESCENT MALES WITH VARICOCELE – A CONTEMPORARY PERSPECTIVE

While an abundance of literature exists on the prevalence and effects of varicocele in the adult population, comparatively few data exist on the effects of varicocele in young males. Given the relatively recent findings linking varicocele to androgen deficiency and hypogonadism, as well as the clearly defined relationship between varicocele and male fertility, a discussion of the effects of varicocele and treatment considerations in adolescent males is appropriate. Varicoceles are found in <1% of prepubertal boys but are diagnosed in 15%–20% of postpubertal 12–18 year old males.<sup>138</sup> The decision to treat varicoceles in the adolescent population is variable and the current best-practice policy on varicocele and infertility from the AUA and American Society for Reproductive Medicine indicates treatment only for adolescents who have varicocele and objective evidence of reduced ipsilateral testicular size.<sup>139</sup> Other indications for varicocele repair in adolescent males include ipsilateral testicular discomfort and semen abnormalities, although these indications are not universally agreed upon.

In young males with varicocele but without testicular discomfort, the decision to treat is a topic of debate, though many believe testicular asymmetry to be a harbinger of testicular dysfunction.<sup>140</sup> Similar to findings in adults, varicocele has been shown to progressively decrease sperm motility and vitality in 17–19 years old untreated males followed with serial semen analyses.<sup>141</sup> A contemporary survey of pediatric urologists found that the majority of pediatric patients with varicoceles are observed, with indications for intervention paralleling those above.<sup>142</sup> Few pediatric urologists consider hypogonadism or androgen deficiency as an indication for varicocelectomy in this population,

highlighting a possible knowledge deficit regarding the link between hypogonadism and varicocele. These findings also highlight the paucity of data evaluating the effects of varicocele in young men.

In the setting of the testicular asymmetry, varicocele repair appears to result in “catch-up” testicular growth and improvement in sperm count.<sup>143</sup> A large 2012 meta-analysis encompassing 14 studies and 1475 patients evaluating the effect of varicocelectomy on testicular catch-up growth in adolescents with testicular volume discrepancy showed a significant reduction in volume differential after varicocelectomy, albeit in the absence of semen analysis data.<sup>144</sup> However, when using testicular size discrepancy as a possible indication for varicocele treatment, one must consider that testicular growth in young men is variable between sides, and a causal link between testicular asymmetry and varicocele cannot definitively be established.<sup>145,146</sup> Thus, the use of testicular volume as a surrogate for global testicular function is inaccurate, and the ultimate impact of varicocele and its treatment on fertility and pregnancy rates in adolescents remains unknown in the absence of longitudinal studies.

Relatively few studies have evaluated the effects of varicocele on semen parameters in young men, although current data do suggest a detrimental effect. A recent meta-analysis evaluated the natural history of varicocele in terms of the effect of varicocele as well as varicocelectomy on semen parameters in males 15–24 years old, finding that across 10 studies encompassing 357 varicocele and 427 control patients, varicocele correlated with decreases in sperm density, motility, and normal morphology.<sup>147</sup> In 10 additional studies encompassing 379 treated and 270 untreated men with varicocele, significant improvements in sperm density and motility were observed in treated men. Together, these results suggest that varicoceles have similar repercussions in adults and young men with respect to fertility, with similar benefits from treatment.

Given that there are ethical considerations in obtaining semen analyses in young males not presenting for fertility evaluation, an alternative approach to assessing testicular function is evaluation of gonadotropin levels. Guarino *et al.* correlated testicular size, gonadotropin levels, and semen parameters in adolescents, finding higher gonadotropin levels in patients with abnormal semen parameters and no correlation with testicular size measurements.<sup>148</sup> In a more recent study, Deshpande *et al.* evaluated the reliability of testicular catch-up growth as a marker of normal testicular function in men 18–27 years old who underwent laparoscopic varicocelectomy between 11 and 16 years old.<sup>149</sup> Using FSH levels, scrotal ultrasonography, and semen analysis, the authors found that an elevated FSH level postoperatively predicts poor testicular function and does not correlate with testicular size. Similar to adults, lower serum inhibin B levels have also been observed in adolescents with varicocele relative to controls in a small study of 16 adolescent males with varicocele and 13 controls.<sup>150</sup> Unlike with the Guarino study, no differences in testosterone, luteinizing hormone or FSH were observed between groups.

No data from adolescent males are currently available supporting a relationship between varicocele and hypogonadism or androgen deficiency. However, a study examining the effects of varicocele repair in men grouped by age found a significant rise in testosterone in men <30 years old, as well as in all other age groups evaluated, after repair, indicating an age-independent effect.<sup>93</sup> Available evidence also indicates that varicocele repair results in testicular growth correlating with increased serum testosterone, supporting the relationship between testicular catch-up growth and a rise in serum testosterone.<sup>95</sup>

While current evidence does not support intervention in cases of adolescent varicocele based on the same criteria used in treating adults,

the growing body of evidence supporting an impact of varicocele on adolescent fertility and testicular function in a time-dependent manner should prompt further study and continued discussion of management practices in the pediatric population.

## CONCLUSION

The impact of varicocele on male fertility continues to grow clearer with additional work, particularly with regards to the positive impact of varicocele repair on semen parameters and pregnancy rates. Integral to this is likely the beneficial molecular effects of varicocele repair on sperm and the testicular microenvironment. As such, our growing understanding of the relationship between varicocele and hypogonadism is likely to benefit from the foundation that studies focused on male infertility have built, and reinforce the molecular effects of varicocele and its treatment in considering patients, particularly younger men, presenting with varicocele. In pediatric populations, relatively little work has linked varicocele to male fertility or semen parameters, but studies suggest that the effects parallel those in adults. With a growing understanding of the pathophysiology and effects of varicocele in both adults and adolescents, treatment guidelines can be adjusted and optimized.

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