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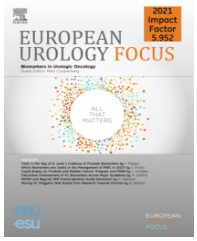

Review - Andrology

Treatment of Persistent or Recurrent Varicoceles: A Systematic Review

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Abstract

Context: The outcomes and morbidity following treatment for persistent or varicocele recurrence remain controversial.
Objective: To conduct a systematic review relating to the outcomes following treatment (any surgical or radiological) for varicocele persistence/recurrence.
Evidence acquisition: A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. Prospective and retrospective observational or interventional studies were included until March 2022. Outcomes were pregnancy rate, improvements in semen parameters after treatment compared with those at baseline, pain control, complication rates, and repeat treatment approach. Men of any age with any-grade persistent/recurrent varicoceles were included.
Evidence synthesis: Of 913 articles identified, 18 with 1073 patients were eligible for inclusion. The mean time between the first and repeat treatment ranged between 5.3 and 73.3 months. The indication for repeat treatment was infertility in eight and pain control in six out of 18 studies, whereas four did not provide details for the indication. Of the patients with recurrent/persistent varicoceles initially treated using a radiological intervention, 83.8% underwent another radiological procedure, whereas 16.2% underwent a surgical procedure. Of those initially treated with a surgical procedure, 77.8% underwent a further surgical procedure, whereas 22.2% underwent a radiological procedure. The rate of success of repeat treatment was 60–100%. The reported complications were as follows: hydrocele (up to 16%), testicular atrophy (up to 2%), scrotal hematoma (up to 1.6%), wound infection (up to 6.6%), chronic pain (up to 2.9%), injury to other organs (up to 10%), and thrombophlebitis (up to 5.8%). The rate of symptom resolution was >90% for pain control. Pregnancy rates were 17–58% at 12-month follow-up. Semen parameters improved after repeat treatment compared with that at baseline in 87.5% of studies. The main limitations are the high risk of bias according to the

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Newcastle and Ottawa Scale, heterogeneity of the included studies, and small simple size.

Conclusions: Treating any grade of persistent/recurrent varicoceles has a good rate of success, pregnancy, and pain control, but there is still a risk of complications. Repeat treatment with the same interventional modality is feasible. The level of evidence is overall low.

Patient summary: In this systematic review on persistent or recurrent varicoceles, we showed that repeat treatment with radiological or surgical procedures was feasible, with good success, pregnancy, and pain control rates at follow-up. However, repeat treatment was associated with a higher risk of complications than reported in the published literature relating to patients having their first intervention.

1. Introduction

The presence of varicoceles is associated with primary and secondary infertility, and sometimes with scrotal pain; however, indications for its treatment are still debatable, as the evidence on its benefit is not unidirectional [1–5]. A proportion of these patients will experience persistence or recurrence of varicoceles after treatment [6,7]. There is currently no uniformly accepted definition for the recurrence and persistence of varicoceles, and the literature on the topic is historically weak. If there is evidence of varicoceles (at clinical examination or imaging, or symptoms) at the first follow-up after treatment, which is usually performed within a year, this may indicate a varicocele persistence. If varicoceles reappear after a negative follow-up after treatment, this may indicate a varicocele recurrence. Rates of varicocele recurrence/persistence vary widely in the literature, depending on the varicocele severity/grade, population under study (children vs adolescents vs adults), technique and approach used (radiological vs microsurgical ligation vs open vs laparoscopic), follow-up length, and definition of persistence or recurrence itself [6,8]. A reason for varicocele recurrence is the persistence of branched spermatic veins that were either not ligated or not embolized during the initial intervention [6]. The management of persistent or recurrent varicoceles can present a challenge, as very few studies have analyzed the functional outcomes, success rates, and complication rates following a repeat intervention. Indeed, guidelines on repeat treatment for persistent or recurrent varicoceles are lacking. Therefore, in this systematic review, we aimed to summarize the published evidence on the causes of persistent or recurrent varicoceles, and the outcomes of repeat treatment in terms of fertility outcomes, symptoms improvement (ie, pain), rates and type of complications, as well as rates of recurrence/persistence of varicoceles after a repeat intervention.

2. Evidence acquisition

2.1. Literature search and inclusion/exclusion criteria

We conducted a systematic review and meta-analysis of all published trials relating to the treatment of persistent and/or recurrent varicoceles. Given the absence of randomized controlled trials (RCTs), retrospective or prospective case series and cohort study were included in the current meta-analysis. Review articles, commentaries, editorials, and articles that did not undergo a peer review were excluded. The review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [9,10]. The meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42022314139).

The PubMed, EMBASE, Web of Science, and Scopus databases were searched for studies indexed up to March 15, 2022. Combinations of the following keywords were used: redo-varicocel*, infertil*, varicocelectomy, radiologic method, pregnancy, recurren*, persisten*, complications, seminal, and sperm alteration. The titles and abstracts of the manuscripts obtained from the search were used to screen for initial study inclusion. A full-text review was performed when the abstract was not sufficient to determine study inclusion. Reference lists of included studies were hand searched for completeness, and if a study was suitable for inclusion, it was included in our systematic review. Four authors completed the study selection independently (G.F., F.B., E.P., and S.T.). Potential disagreements were resolved by consensus among all coauthors.

2.2. Inclusion and exclusion criteria

All studies including males of any age, treated for any-grade recurrent or persistent varicoceles, were included in the current systematic review and meta-analysis. Studies with incomplete baseline data regarding baseline age at repeat treatment and the type of repeat treatment were excluded.

2.3. Data extraction

Data were collected according to a proforma that included the year of publication; authors' names; study design; number of participants included; number of treated and, in the case of the control observational arm, untreated men; presence of recurrent or persistent varicoceles; grade, side, and cause of the varicocele persistence/recurrence; mean age at repeat treatment; type of first treatment; type of repeat treatment, categorization as retrograde or anterograde embolization/sclerotherapy (radiological), open or laparoscopic high ligation, and inguinal or subinguinal (microscopic) ligation; median follow-up (months); pregnancy rates; semen parameters, that is, sperm count, sperm concentration, progressive motility, and morphology at baseline and after treatment/end of follow-up; hormonal profile at baseline and after treatment/end of follow-up;

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rates of symptom improvement/resolution; rates and type of complications; as well as the rates of recurrence/persistence of the varicoceles after repeat treatment.

2.4. Data analysis

The risk of bias (RoB) was determined using the Newcastle and Ottawa Scale for nonrandomized studies independently by four authors (G.F., F.B., E.P., and S.T.) [11,12]. Only a qualitative synthesis of the included studies was possible given the high inconsistency of quantitative data that hindered any meta-analysis.

3. Evidence synthesis

Of 913 articles identified, 18 were eligible according to our inclusion criteria, involving 1073 patients (Fig. 1). Table 1 summarizes the characteristics of the included studies. The oldest study was published in 1983 and the most recent one in 2021. Overall, the RoB according to the Newcastle and Ottawa Scale ranged from high risk to very high risk (Supplementary Table 1).

The mean (range) age at repeat treatment was 26.3 (12.6–55.0) yr. The mean (range) time between first and repeat treatment was 24.1 (5.3–71.7) mo. Regarding laterality of the varicocele recurrence or persistence, of 1073 patients, data were available for 753 cases, of which 506 (67.2%) had a left varicocele, 240 (31.9%) a bilateral varicocele, and seven (0.9%) isolated right varicoceles.

Figure 2 represents the main modalities of repeat treatments. Data on initial varicoceles treatment were available for 917 cases, of which 849 (92.6%) were initially treated surgically (n = 543, 63.9%) with an inguinal or subinguinal surgical approach and 237 (27.9%) with retroperitoneal high ligation — for 69 (8.1%) cases it was not specified - and 68 (7.4%) initially underwent anterograde or retrograde sclerotherapy/embolization. Overall, of those with recurrent/persistent varicoceles initially undergoing radiological treatment, 57 (83.8%) underwent a further radiological procedure, whereas 11 (16.2%) underwent a surgical procedure; of those with recurrent/persistent varicoceles initially undergoing a surgical procedure, 657 (77.8%) underwent a further surgical procedure, whereas 187 (22.2%) underwent a radiological procedure.

The indication for repeat treatment was persistent infertility in eight out of 18 studies, and persistent pain control in six out of 18 studies, whereas four studies stated that the indication for repeat treatment was resolution of varicoceles without giving any further clinical information.

3.1. Summary of included studies

The results of individual studies are summarized in Table 1.

Kaufman et al [13] retrospectively analyzed the cause and the repeat treatments of eight consecutive patients with recurrent varicoceles after surgical ligation or balloon occlusion of the internal spermatic vein. Retreatment with embolization of collateral veins was found to be an effective treatment in six out of eight patients, who did not demonstrate further recurrences during follow-up (maximum 24 months of follow-up).

Murray et al [14] retrospectively investigated the patterns of spermatic collateral veins causing recurrent varicoceles in 44 consecutive patients by the use of venography. Surgical recurrences were treated with percutaneous balloon occlusion, but up to 39% of cases were not anatomical candidates for repeat percutaneous occlusion. Complications were not reported.

Punekar et al [15] reviewed 39 consecutive patients with postsurgical recurrent varicoceles who underwent anterograde bilateral internal spermatic venography and treated with embolization. The rate of success was 85% (n = 33 patients), while 15% of cases (n = 6) had persistent varicoceles. In addition, for patients with available follow-up (n = 28), sperm count and motility improved significantly in 16 (57.1%) cases after repeat treatment at 6-month follow-up. Five patients (18%) achieved pregnancy during follow-up. Complications were not reported.

Madjar et al [16] in 1997 retrospectively analyzed the outcome of subinguinal ligation of spermatic veins in 23 consecutive patients after previous surgical treatment. After 1 year of follow-up treatment, success was achieved in 21 patients (91.3%). During follow-up, there were no signs of clinical or radiologic recurrence. Sperm count and motility were improved after successful treatment. One case of hydrocele was reported as a complication after subinguinal ligation.

The work from Mazzoni et al [17] analyzed the results of anterograde embolization for recurrent varicoceles after either surgical ligation or radiological embolization in 53 consecutive patients followed up for a mean of 9 months. Although four patients were lost to follow-up, the procedure was clinically successful in 47 (95.9%) cases, and only two recurrences were reported, which were subsequently treated with high retroperitoneal ligation. Complications were not observed.

Grober et al [18] retrospectively examined the effectiveness of subinguinal microsurgical varicocelectomy in the treatment of persistent or recurrent varicoceles following surgical repair in 54 consecutive patients. The median sperm concentration, percent motility, total motile sperm per ejaculate, and mean total serum testosterone improved significantly following recurrent varicocelectomy at mean 9months follow-up. Pregnancy rate was 40%, considering both spontaneous and medically assisted pregnancy. Complications were not observed.

Flati et al [19] retrospectively reported fertility outcomes of 34 consecutive infertile men with recurrent varicoceles after inguinal varicocelectomy or embolization, submitted to spermaticoepigastric microsurgical shunt drainage. Complete resolution of the varicoceles was reported in 33 (97.0%) patients; however, a significant improvement in sperm concentration was observed only in the youngest patients (below 30 year of age), while sperm motility increased across all age groups. Overall, 11 (32.3%) couples achieved pregnancy in 1 year follow-up after the procedure. Regarding complications, one case of hydrocele, two cases of persistent testicular pain, and one case of incomplete resolution of the varicoceles were observed.

In 2005, Chawla et al [20] retrospectively investigated the results of microsurgical inguinal varicocelectomy in 12 consecutive patients with recurrent varicoceles after failed varicocelectomy and scrotal pain/discomfort. A favorable outcome was seen in ten (90.9%) patients, with six reporting complete pain relief and four reporting pain improvement compared with baseline. One case of hydrocele was reported as a complication.

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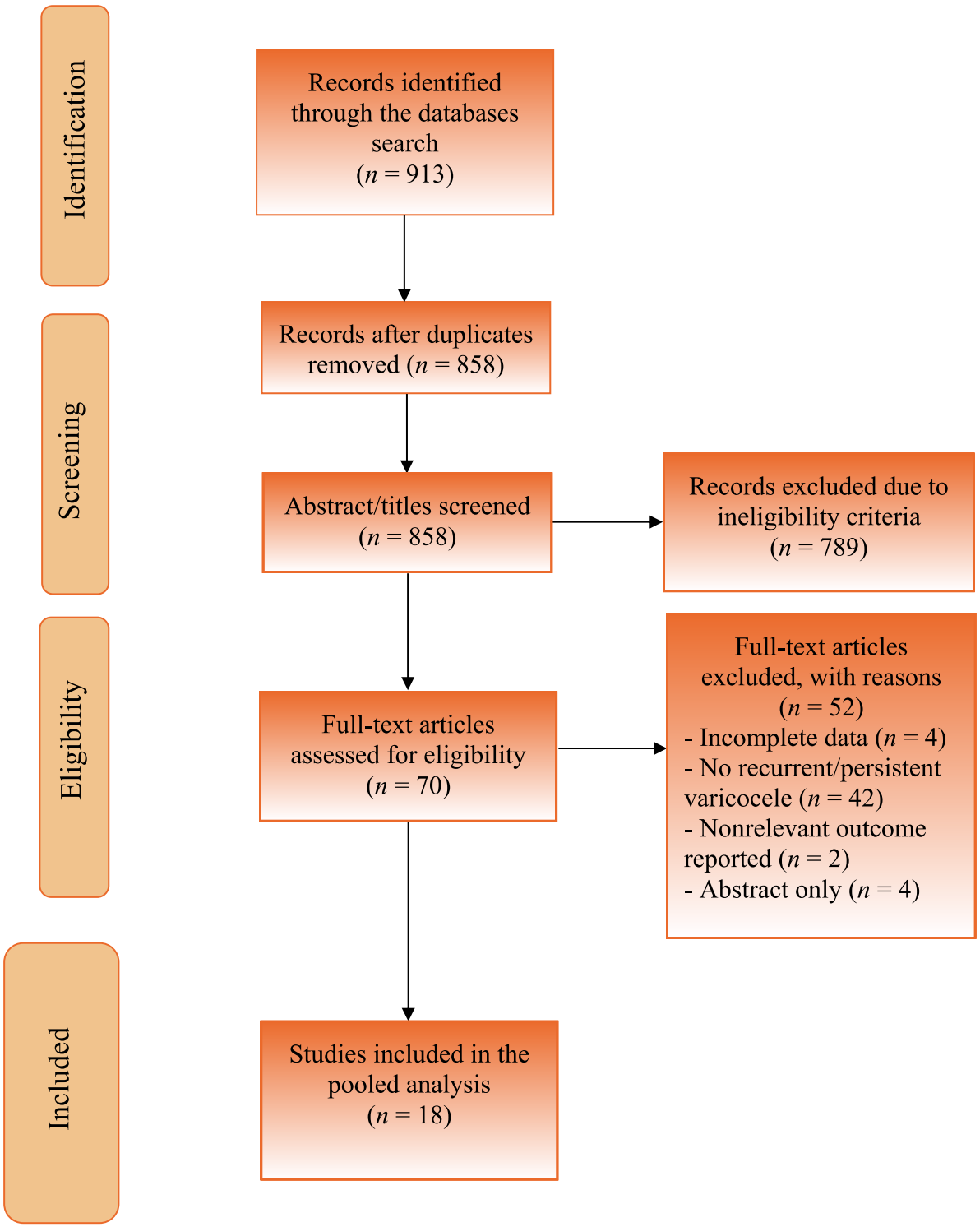

Fig. 1 – PRISMA flow diagram for study selection according to inclusion and exclusion criteria. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Sze et al [21] assessed the mechanism of persistent or recurrent varicoceles after surgical repair by examining the venographic anatomy and corrected them with embolization. Of 17 patients, 11 (65%) were found to have duplication draining into a single left gonadal vein, mostly in the pelvis and the inguinal canal. Embolization was successful in treating all cases, without any further persistent or recurrent varicoceles found during follow-up at 6 month. One case of thrombophlebitis was reported as a complication.

In 2011, Glassber et al [22] published their retrospective monocentric cases series including 19 boys (16.5 [range 12.6–22.0] submitted to repeat varicocelectomy [16 open, one laparoscopic, and two radiographic embolization]).

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Table 1 – Summary of characteristics of the included studies

First author	Year of publication	Study design	No. of patients enrolled	Length of follow-up	Mean age	Causes of varicocele treatment failure	Indication for repeat treatment	Type of repeat treatment	Outcome measure
Kaufman et al [13]	1983	Retrospective case series	8	Range: 12–24 mo	NR	Unligated/untreated internal spermatic veins	Subfertility and pain	Embolization	Clinical resolution: 6 out of 8 patients (75%)
Murray et al [14]	1986	Retrospective case series	44	NR	NR	Collateral spermatic vein	NR	Embolization	Clinical resolution in 96% of postoperative recurrences and 61% post–balloon occlusion recurrences
Punekar et al [15]	1996	Retrospective case series	39	Up to 12 mo	NR	Dilated internal or external spermatic veins	Infertility	Retrograde embolization	Clinical resolution in 33 (86%) of patients Semen parameters: motility improved in 3 (11%) and count in 16 (57%) out of 28 patients Pregnancy: 5 (17%) out of 28 couples
Madjar et al [16]	1998	Retrospective case series	23	At least 6 mo	NR	NR	Infertility	Subinguinal varicocelectomy	Clinical resolution: 21 patients (91%) Semen parameters: 19 patients (83%) improved Complications: 1 hydrocele case (4%)
Mazzoni et al [17]	2002	Retrospective case series	53	9 mo	NR (range 11.0–38.0)	NR	Subfertility	Antegrade sclerotherapy	Clinical resolution: 47 patients (96%) Complications: 0 (0%)
Grober et al [18]	2004	Retrospective case series	54	9 mo (range: 0.5–91)	31.5 (range 16–52)	NR	Infertility and pain	Microsurgical subinguinal varicocelectomy	Semen parameters: sperm concentration, morphology, and motility improved (all $p < 0.05$) Pregnancy: 14 out of 35 patients (40%) Sex hormone: total testosterone increased ($p < 0.05$) Complications: 0 (0%)
Flati et al [19]	2004	Retrospective case series	34	8.5 yr (range: 0.5–16)	NR	Dilated spermatic veins	Infertility	Microsurgical shunt drainage (spermatic-epigastric vein)	Clinical resolution: 33 patients (97%) Semen parameters: a significant improvement in sperm concentration only in patients <30 yr of age, sperm motility improved overall Pregnancy: 11couples (32%) Pain resolution: 33 patients (97%) Complications: 1 case of hydrocele (3%), 2 cases of persistent testicular pain (6%), and 1 incomplete resolution (3%)
Chawla et al [20]	2005	Retrospective case series	11	12 mo (range: 3–32)	NR	NR	Pain	Microsurgical subinguinal varicocelectomy	Pain control: improvement/resolution in 10 patients (90.9%) Complications: 1 case of hydrocele (9%)
Sze et al [21]	2008	Retrospective case series	17	6 mo	25 (range 13–54)	Dilated or duplicated spermatic veins	Infertility and pain	Anterograde embolization	Clinical resolution: 17 patients (100%) Semen parameters: increase in sperm count Complications: 1 case of thrombophlebitis (6%)
Glassberg et al [22]	2011	Retrospective case series	19	25.3 mo (range: 6–53)	16.5 (range 12.6–22.0)	Dilated spermatic veins	Reduced testicular volume	Microsurgical subinguinal varicocelectomy ($n = 16$), laparoscopic varicocelectomy ($n = 1$), embolization ($n = 2$)	Clinical resolution: 17 patients (100%) of the surgical group, 1 (50%) of the radiological group Doppler US parameters Complications: 3 case of hydrocele (16%), 1 case of testicular atrophy (5%)
Kim et al [23]	2012	Retrospective case series	28	6.5 mo (range: 0–54)	19.5 (range 13–55)	Dilated internal spermatic veins	Pain/ symptoms	Embolization	Clinical resolution: 26 patients (93%) Pain control: 11 out of 12 patients (92%) Complications: 0 (0%)

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Table 1 (*continued*)

First author	Year of publication	Study design	No. of patients enrolled	Length of follow-up	Mean age	Causes of varicocele treatment failure	Indication for repeat treatment	Type of repeat treatment	Outcome measure
Moon et al [24]	2012	Retrospective case series	15	23 mo	21.2 (range 12.0–42.0)	NR	Not clear	Retrograde embolization (7); subinguinal varicocelectomy (8)	Clinical resolution: 15 patients (100%) Semen parameters: not statistically significant improvement Complications: 0 (0%)
Chen [25]	2014	Retrospective case series	48 total: 38 microsurgical subinguinal, 10 observation	Range: 6–12 mo	34 (NR)	Dilated spermatic veins (86.8%)	Infertility	Microsurgical subinguinal varicocelectomy	Semen parameters: 21 patients (55%) Pregnancy: 5 out of 38 patients (13%) Sex hormone profile: not statistically significant improvement in testosterone Complications: 2 cases of hydrocele (5%)
Jargiello et al [26]	2013	Retrospective case series	31	14 mo (range: 7–32)	20.5 (range 13–32)	Dilated spermatic veins	Infertility and pain	Embolization	Clinical resolution: 31 patients (100%) Semen parameters: improvement in 10 patients Complications: 0 (0%)
Yan et al [27]	2016	Retrospective case series	64	12 mo	24.4 (SD 5.4)	NR	Infertility	Transumbilical single-port laparoscopic varicocelectomy (34) Retroperitoneal ligation (30)	Pregnancy: 36 patients (57%) Complications: 18 case of recurrence (28%), 4 cases of hydrocele (6%), 2 cases of testicular artery injury (3%), 4 cases of injury to other organs (6%), 3 cases of infection (5%)
Çift and Yucel [28]	2018	Retrospective case series	28	15 mo (6–36)	31 (SD 3.8)	NR	Pain	Microsurgical subinguinal varicocelectomy	Pain control: improvement in mean VAS score Complications: 1 case of recurrence (4%), 1 case of hydrocele (4%)
Çayan and Akbay [29]	2018	Retrospective case series	217 total: 120 microsurgical subinguinal, 97 observation	27.6 ± 14.8 mo	32.4 (SD 5.9)	Dilated external spermatic vein and unligated internal spermatic veins (56.3%) Unligated internal spermatic veins (37.9%) Dilated external spermatic veins (5.8%)	Infertility	Microsurgical subinguinal varicocelectomy	Semen parameters: total motile sperm count increased Pregnancy (spontaneous or MA): 63 patients (52.3%) Sex hormone profile: total testosterone increased ($p < 0.05$) Complications: 2 cases of scrotal hematomas (2%)
Park et al [30]	2021	Retrospective registry based	340	NR	30.3 (SD 14.9)	NR	Not clear	Inguinal varicocelectomy (146); microsurgical subinguinal varicocelectomy (85); abdominal open varicocelectomy (27); abdominal lps varicocelectomy (24) Embolization (58)	NR

lps = laparoscopic; MA = medically assisted; NR = not reported; SD = standard deviation; US = ultrasound scan; VAS = visual analog scale.
The definition of clinical resolution varies across the studies, including no evidence of further varicoceles at follow-up examination/US, and no persistence of testicular symptoms or sperm alteration.

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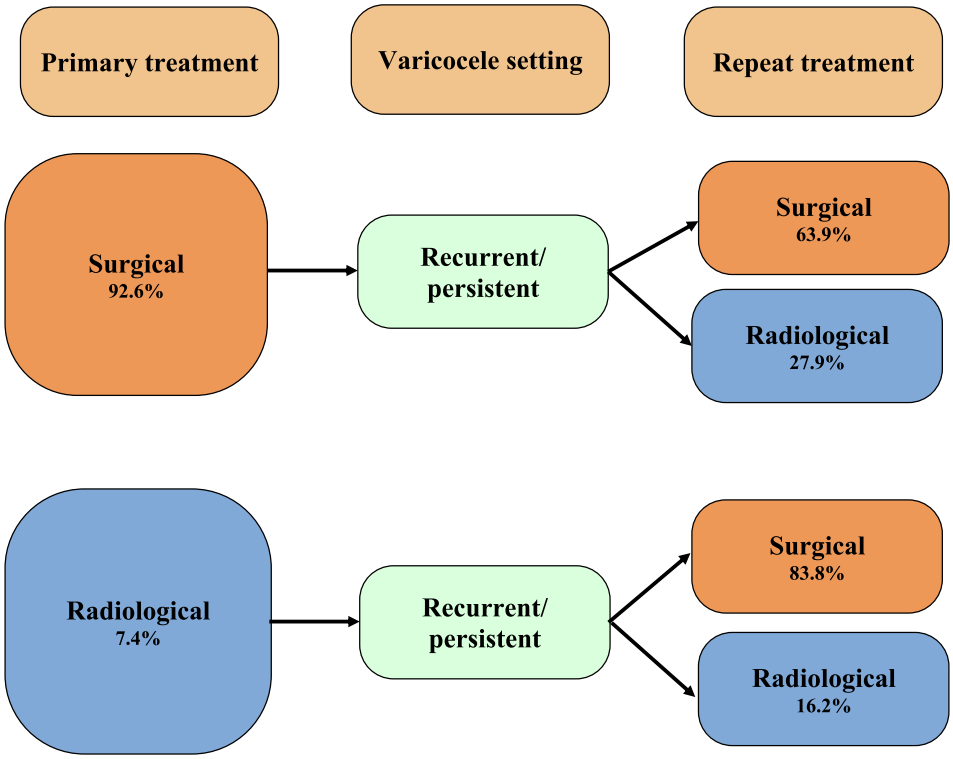

Fig. 2 – Flow diagram depicting repeat treatment for persistent or recurrent varicoceles according to the primary treatment approach (radiological vs surgical). Data were available for only 916 patients (15 out of 18 included studies).

They confirmed good postoperative outcomes at an intermediate point of follow-up (mean 23.4 months), with no failure in the surgically treated patients, but in one out of two in those treated radiologically. One patient had decreased postoperative testicular volume, and three developed a hydrocele following repeat treatment.

Kim et al [23] retrospectively assessed, over a 10-year period 28 patients, with recurrent or persistent varicoceles with pain, treated with retrograde transcatheter embolization. Patients had previously been submitted to laparoscopic varicocelectomy (39.3%), high retroperitoneal ligation (25%), or inguinal ligation (25%). Success in varicocele repeat treatment was achieved in 26 (92.6%) cases, and a suspected thrombophlebitis was the only complication reported. Pain was relieved in 50% of cases and improved in 33.3%.

In 2012, Moon et al [24] retrospectively reported a case series with 15 patients with recurrent varicoceles initially treated with embolization or subinguinal varicocelectomy. Repeat treatments were reported to be effective in all the cases, and sperm count increased after repeat treatment; however, statistical significance was not reached. No complications were observed.

Chen [25] conducted a retrospective case series study of patient with recurrent varicoceles. Semen parameters did not improve in 55% of cases. Factors associated with a successful repeat varicocelectomy were lower follicle-stimulating hormone (FSH) levels and peak retrograde flow at Doppler scan, longer time to recurrent varicoceles, larger testicular volume preoperatively, and a higher number of ligated veins during repeat varicocelectomy. No recurrences were noticed, but two cases of hydrocele were reported at 1 yr from repeat treatment.

Jargiello et al [26] retrospectively described the venographic findings in 33 patients with postsurgical recurrent varicoceles and assessed the efficacy of the subsequent minimally invasive endovascular treatment. Retrograde embolization was successful in all 31 cases, and no complications were observed during a mean follow-up of 14 mo.

Yan et al [27] assessed the efficacy of laparoscopic varicocelectomy (n = 34 patients) compared with traditional retroperitoneal ligation (n = 30) for recurrent varicoceles. They found that the periprocedural complication rates were considerably lower in the laparoscopic groups, with higher risks of infection, damage to abdominal organs, and hydrocele in case of traditional retroperitoneal ligation. There was, however, no difference in terms of pregnancy rates at 12-month follow-up. Recurrence rate after repeat treatment was around 40% for traditional retroperitoneal ligation and around 17.6% for laparoscopic varicocelectomy (p = 0.047).

In the study by Çift and Yucel [28], retrospective data from 27 patients with recurrent varicoceles after ligation (diagnosed with Doppler ultrasound) retreated with microsurgical subinguinal varicocelectomy were analyzed. Complete resolution, partial resolution, and nonresponsiveness of symptoms were found, respectively, in 88.8%, 7.5%, and 3.7% at 6 mo postoperatively. In addition, the reduction of pain score was higher for those who had grade 3 than for those who had grade <3 varicoceles. No complications or worsening of symptoms was reported.

Çayan and Akbay [29] reported the results from a retrospective cohort study on 120 men (190 sites) submitted to

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microsurgical subinguinal repeat varicocelectomy and 97 to observation (control group). Primary varicocele surgeries included macroscopic inguinal or subinguinal approach in 88 patients (73.3%), high ligation (Palomo technique) in 26 patients (21.7%), and microsurgical inguinal or subinguinal approach in six patients (5%) in the microsurgical varicocelectomy group, and in 73 (75.2%), 21 (21.6%), and three (3.1%) patients in the control group, respectively. After a median follow-up of almost 2 years, the total motile sperm count, testosterone levels, and spontaneous and overall pregnancy rates were higher in the microsurgical repeat varicocelectomy group than in the control group. Only two scrotal hematomas were reported in the treatment group.

Park et al [30] recently published a registry-based retrospective observational cohort study including 340 patients submitted to repeat varicocelectomy, for either pain or infertility. Inguinal, microscopic, embolization, abdominal, and laparoscopic surgery were used for repeat treatment in 43%, 25%, 16%, 8%, and 7%, respectively. The authors concluded that most patients who initially underwent microscopic varicocelectomy or embolization underwent repeat varicocelectomy using the same method. Being a registry-based study, they did not report seminal, pregnancy, or pain outcomes after redo treatment.

3.2. Success and complication rates

Success rate, that is, rates of resolution of recurrence or persistence of varicoceles after repeat treatment, ranged from 60% to 100%. Six studies did not report success rates of repeat treatment [15,16,21,22,27,30]. The complications most frequently reported were hydrocele (ranging from 0% to 16%) [16,19,20,22,25,27–29], testicular atrophy (0–5.2%) [22,26,27], scrotal hematoma (0–1.6%) [29], wound infection (0–6.6%) [27], chronic pain (0–2.9%) [19], and injury to other organs (in case of laparoscopic or retroperitoneal high ligation; up to 10% of cases) [27]. In addition, in the case of radiological embolization, thrombophlebitis was reported in up to 5.8% of cases [15,17,21,23,24,26]. Two studies did not analyze complication rates after repeat treatment [22,30].

3.3. Causes of varicocele persistence/recurrence

Causes of persistent or recurrent varicoceles are reported inconstantly, with different definitions and mostly without providing the exact number and proportion of cases relative to the specific cause. The presence of variant collateral veins that bypassed the point of occlusion during sclerotization/embolization or ligation has been reported by some authors. These collateral veins have been found to originate and terminate within the internal spermatic vein in the retroperitoneum or low inguinal canal (mid or low collateral) [13,14,16,25,29]. Another possibility described was the presence of collateral veins originating from the internal spermatic vein below the site of occlusion and draining directly into the renal vein or into its branches, or more rarely draining directly into the inferior cava or the internal iliac vein (high and low collateral, respectively) [13–16,25]. Scrotal collateral were rarely reported [13–16]. Other possible suggested cause of recurrent or persistent varicoceles is reflux in the cremasteric external pudendal or gubernacular veins, which all drains into the internal iliac vein [23,24,29].

3.4. Pregnancy and semen parameters

Pregnancy outcomes were analyzed in six studies out of the 18 included in this systematic review [15,22,25,27–29]. Pregnancy rates at a maximum follow-up of 12 months ranged from 17% to 58% in the treated groups. Studies including a control, untreated arm reported a pregnancy rate ranging from 0% to 39.2% [25,29]. Regarding semen parameters, results were reported in eight out of the 18 included studies, and in seven of them some improvements were demonstrated compared with baseline values [15,18,19,21–23,25,29]. Only in one study, the differences in sperm count, morphology, and motility were not statistically significantly different from those at baseline. In addition, the proportion of patients who had improvement in at least one seminal parameter after treatment was around 30% of all the patients with recurrent/persistent varicoceles submitted to repeat treatment; however, these results were reported only in a few studies.

3.5. Hormone profile

Hormone profile was analyzed in only two studies. Total testosterone improved after repeat treatment in one study [29] and not in the other one assessing hormone profile [25]. In the latter, however, an improvement in FSH was found after re-retreatment.

3.6. Pain relief

In seven out of the 18 studies, patients reported scrotal or testicular pain at baseline before repeat treatment for recurrent/persistent varicoceles. Out of the seven studies, three reported a follow-up on pain control after repeat treatment, and the rate of symptom resolution was as high as 90% [20,23,28].

3.7. Discussion

3.7.1. Principal findings

In this systematic review on repeat treatment for persistent or recurrent varicoceles, we highlighted several clinically meaningful results. First, in approximately 80% of cases, the therapeutic approach, either surgical or radiological, for recurrent or persistent varicoceles was the same as in the initial treatment. The mean time between initial and repeat treatment was around 2 years. The success rate was high, between 60% and 100%; however, there is a risk of complications, including scrotal hematoma, chronic pain, testicular atrophy, adjacent organ injury, and hydrocele in up to 16% of cases. Only two studies compared pregnancy outcomes between treated and observed groups of patients with persistent or recurrent varicoceles, showing an advantage for the treatment group. In addition, in most studies, semen analysis was improved significantly after retreatment. Pain relief was analyzed in only three studies, and in as high as 90% of cases, repeat treatment improved or resolved symptoms. Finally, serum testosterone level was analyzed in two studies, with only one reporting a significant improvement.

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3.7.2. Limitations

Unfortunately, the RoB and heterogeneity among the included studies, in terms of treatment provided, population characteristics, type and timing of varicocele assessment, outcome definitions and assessment, and length of follow-up after retreatment, were high. This prevented us from performing a quantitative meta-analysis, and we were able to provide only a summary of the results for each outcome. In addition, the lack of RCTs and the inclusion of only retrospective case series, where the risk of information and selection biases are high, weakened the evidence provided in this meta-analysis. In addition, the majority of the case series included in the current systematic review lacked a proper control/observation arm, meaning that a fair comparison between observed and treated patients with persistent/recurrent varicoceles in terms of fertility outcomes and pain control over the long-term follow-up is missing. In addition, although a few works compared different therapeutic approaches for recurrent or persistent varicoceles, the small number and the different approaches in different centers, or even in the same centers over the years, made it impossible to perform a clinically and statistically meaningful comparison among different treatment approaches for persistent or recurrent varicoceles. In addition, the lack of data on stratification of persistent/recurrent varicocele grading, and on the outcomes of their treatment, creates a void in clinical knowledge that deserves to be filled.

4. Conclusions

Repeat treatment for persistent or recurrent varicoceles is feasible, and the rates of success are high. Further treatment failure was low, and outcomes for pain control and/or fertility were good. However, when counseling patients regarding repeat treatment options, a high rate of complications should be discussed. Finally, the RoBs of the included studies are high, so the level of evidence of the efficacy and safeness of repeat treatment for varicocele persistence or recurrence is low.

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Study concept and design: Fallara, Castiglione, Muneer.
Acquisition of data: All authors.
Analysis and interpretation of data: Fallara, Tang, Pang.
Drafting of the manuscript: Fallara, Tang, Pang, Muneer, Salonia.
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Appendix A. Supplementary data

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References

[1] Persad E, O'Loughlin CA, Kaur S, et al. Surgical or radiological treatment for varicoceles in subfertile men. Cochrane Database Syst Rev 2021;2021:CD000479.
[2] Minhas S, Bettocchi C, Boeri L, et al. European Association of Urology guidelines on male sexual and reproductive health: 2021 update on male infertility. Eur Urol 2021;80:603–20.
[3] Wilne S, Cape J, Eastwood A, et al. Fertility problems: assessment and treatment. https://www.nice.org.uk/guidance/conditions-and-diseases/fertility–pregnancy-and-childbirth.
[4] Fallara G, Cazzaniga W, Boeri L, et al. Male factor infertility trends throughout the last 10 years: report from a tertiary-referral academic andrology centre. Andrology 2021;9:610–7.
[5] Fallara G, Capogrosso P, Pozzi E, et al. The effect of varicocele treatment on fertility in adults: a systematic review and meta-analysis of published prospective trials. Eur Urol Focus 2022. https://doi.org/10.1016/j.euf.2022.08.014, In press.
[6] Rotker K, Sigman M. Recurrent varicocele. Asian J Androl 2016;18:229–33.
[7] Lotti F, Maggi M. Ultrasound of the male genital tract in relation to male reproductive health. Hum Reprod Update 2015;21:56–83.
[8] Çayan S, Orhan İ, Akbay E, Kadıoğlu A. Systematic review of treatment methods for recurrent varicoceles to compare post-treatment sperm parameters, pregnancy and complication rates. Andrologia 2019;51:e13419.
[9] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[10] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.
[11] Armijo-Olivo S, Stiles CR, Hagen NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. J Eval Clin Pract 2012;18:12–8.
[12] Lo C-K-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol 2014;14:45.
[13] Kaufman SL, Kadir S, Barth KH, Smyth JW, Walsh PC, White RI. Mechanisms of recurrent varicocele after balloon occlusion or surgical ligation of the internal spermatic vein. Radiology 1983;147:435–40.
[14] Murray RR, Mitchell SE, Kadir S, et al. Comparison of recurrent varicocele anatomy following surgery and percutaneous balloon occlusion. J Urol 1986;135:286–9.
[15] Punekar SV, Prem AR, Ridhorkar VR, Deshmukh HL, Kelkar AR. Post-surgical recurrent varicocele: efficacy of internal spermatic venography and steel-coil embolization. Brit J Urol 1996;77:124–8.
[16] Madjar S, Moskovitz B, Issaq E, Weinberger M, Nativ O. Low inguinal approach for correction of recurrent varicocele. Int Urol Nephrol 1998;30:69–73.
[17] Mazzoni G, Minucci S, Gentile V. Recurrent varicocele: role of antegrade sclerotherapy as first choice treatment. Eur Urol 2002;41:614–8.
[18] Grober ED, Chan PTK, Zini A, Goldstein M. Microsurgical treatment of persistent or recurrent varicocele. Fertil Steril 2004;82:718–22.
[19] Flati G, Porowska B, Flati D, Veltri S, Sportelli G, Carboni M. Improvement in the fertility rate after placement of microsurgical shunts in men with recurrent varicocele. Fertil Steril 2004;82:1527–31.

[20] Chawla A, Kulkarni G, Kamal K, Zini A. Microsurgical varicocelectomy for recurrent or persistent varicoceles associated with orchalgia. Urology 2005;66:1072–4.
[21] Sze DY, Kao JS, Frisoli JK, McCallum SW, Kennedy WA, Razavi MK. Persistent and recurrent postsurgical varicoceles: venographic anatomy and treatment with N-butyl cyanoacrylate embolization. J Vasc Interv Radiol 2008;19:539–45.
[22] Glassberg KI, Badalato GM, Poon SA, Mercado MA, Raimondi PM, Gasalberti A. Evaluation and management of the persistent/recurrent varicocele. Urology 2011;77:1194–8.
[23] Kim J, Shin JH, Yoon HK, et al. Persistent or recurrent varicocoele after failed varicocoelectomy: outcome in patients treated using percutaneous transcatheter embolization. Clin Radiol 2012;67:359–65.
[24] Moon KH, Cho SJ, Kim KS, Park S, Park S. Recurrent varicoceles: causes and treatment using angiography and magnification assisted subinguinal varicocelectomy. Yonsei Med J 2012;53:723–8.
[25] Chen S-S. Predictive factors of successful redo varicocelectomy in infertile patients with recurrent varicocele. Andrologia 2014;46:738–43.
[26] Jargiello T, Drelich-Zbroja A, Falkowski A, Sojka M, Pyra K, Szczerbo-Trojanowska M. Endovascular transcatheter embolization of recurrent postsurgical varicocele: anatomic reasons for surgical failure. Acta Radiol 2013;56:63–9.
[27] Yan T-Z, Wu X-Q, Wang Z-W. Treatment effect of TUSPLV on recurrent varicocele. Exp Ther Med 2017;13:45–8.
[28] Çift A, Yucel MO. Outcomes of microsurgical subinguinal varicocelectomy to treat painful recurrent varicocele. Andrologia 2018;50:e13105.
[29] Çayan S, Akbay E. Fate of recurrent or persistent varicocele in the era of assisted reproduction technology: microsurgical subinguinal redo varicocelectomy versus observation. Urology 2018;117:64–9.
[30] Park HK, Min GE, Chung KJ, Li S, Choi WS, Chung BI. Practice pattern of redo varicocelectomy for recurrent varicocele according to type of initial treatment: retrospective analysis of a United States-based insurance claims database. World J Mens Heal 2021;39:559–65.

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