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**Original Article**
**Male reproductive health and infertility**

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health Published online Jun 22, 2023
https://doi.org/10.5534/wjmh.230034

The World Journal of MEN's HEALTH

# Does Varicocele Repair Improve Conventional Semen Parameters? A Meta-Analytic Study of Before-After Data

Rossella Cannarella[1,2], Rupin Shah[3], Taha Abo-Almagd Abdel-Meguid Hamoda[4,5], Florence Boitrelle[6,7], Ramadan Saleh[8], Murat Gul[9], Amarnath Rambhatla[10], Parviz Kavoussi[11], Tuncay Toprak[12], Ahmed M. Harraz[13,14,15], Edmund Ko[16], Gökhan Çeker[17], Damayanthi Durairajanayagam[18], Noora Alkahidi[19], Shinnosuke Kuroda[2,20], Andrea Crafa[1], Ralf Henkel[21,22], Gianmaria Salvio[23], Berk Hazir[24], Mahsa Darbandi[25,26], Marion Bendayan[6,7], Sara Darbandi[25,26], Marco Falcone[27], Nicolas Garrido[28], Raghavender Kosgi[29], Raneen Sawaid Kaiyal[2], Keshab Karna[30], Nguyen Ho Vinh Phuoc[31,32], Ponco Birowo[33], Giovanni M. Colpi[34], Jean de la Rosette[35], Germar-Michael Pinggera[36], Quang Nguyen[37,38], Armand Zini[39], Wael Zohdy[40], Rajender Singh[41], Pallavi Saini[42], Sidney Glina[43], Haocheng Lin[44], Taymour Mostafa[40], Cesar Rojas-Cruz[45], Mohamed Arafa[40,46,47,48], Aldo E. Calogero[1], Fotios Dimitriadis[49], Priyank Kothari[50], Vilvapathy Senguttuvan Karthikeyan[51], Keisuke Okada[52], Koji Chiba[52], Ates Kadıoglu[53], Baris Altay[54], Tahsin Turunc[55], Birute Zilaitiene[56], Fatih Gokalp[57], Aram Adamyan[58], Darren Katz[59,60,61], Eric Chung[62], Tiago Cesar Mierzwa[43], Daniel Suslik Zylbersztejn[63], Gustavo Marquesine Paul[64], Nikolaos Sofikitis[65], Ioannis Sokolakis[66], Vineet Malhotra[67], Sakti Ronggowardhana Brodjonegoro[68], Ricky Adriansjah[69], Akira Tsujimura[70], Toshiyasu Amano[71], Giancarlo Balercia[23], Imad Ziouziou[72], Isaac Ardianson Deswanto[73], Marlon Martinez[74], Hyun Jun Park[75,76], Mustafa Emre Bakırcıoglu[77], Erman Ceyhan[78], Kaan Aydos[79], Jonathan Ramsay[80], Suks Minhas[81], Manaf Al Hashimi[82,83], Ramy Abou Ghayda[84], Nicholas Tadros[85], Puneet Sindhwani[86], Christopher C.K. Ho[87], Rinaldo Indra Rachman[33], Marcelo Rodriguez Pena[88], Ahmad Motawi[40], Arun Karthik Ponnusamy[89], Satish Dipankar[90], Azwar Amir[91], Saleh Binsaleh[92], Ege Can Serefoglu[93], Ravi Banthia[94], Kareim Khalafalla[47,95,96], Ari Basukarno[97], Nguyen Hoai Bac[98], Karun Singla[99], Rafael F. Ambar[43,100], Konstantinos Makarounis[101], Shivam Priyadarshi[102], Gede Wirya Kusuma Duarsa[103], Widi Atmoko[33], Sunil Jindal[104], Eko Arianto[105], Hamed Akhavizadegan[106], Haitham El Bardisi[47,48], Ohad Shoshany[107], Gian Maria Busetto[108], Mohamad Moussa[109], Mounir Jamali[110], Mohamed S. Al-Marhoon[111], Mikhail Ruzaev[112], Hasan M. A. Farsi[4], Shingai Mutambirwa[113], Dong Sup Lee[114], Deniz Kulaksiz[115], Yu-Sheng Cheng[116], Abderrazak Bouzouita[117], Selcuk Sarikaya[118], Hussein Kandil[119], Georgios Tsampoukas[120], Ala'a Farkouh[121], Kasonde Bowa[122], Missy Savira[33], Nasser Mogharabian[123], Tan V. Le[31,32], Maruto Harjanggi[124], Dang Tuan Anh[125], Tran Quang Tien Long[126], Mohammad Ayodhia Soebadi[127], Lukman Hakim[128], Marko Tanic[129], Umut Cagin Ari[130], Firuza R. Parikh[131], Gokhan Calik[35], Vinod KV[132], Gyem Dorji[133], Andri Rezano[134,135],

**Received:** Feb 14, 2023 **Accepted:** Feb 28, 2023 **Published online** Jun 22, 2023
**Correspondence to:** Ashok Agarwal https://orcid.org/0000-0003-0585-1026
Global Andrology Forum, 130 West Juniper Lane, Moreland Hills, OH 44022, USA.
**Tel:** +1-216-312-5829, **E-mail:** Agarwal@globalandrology.org, **Website:** https://www.globalandrologyforum.com
*All authors are members of the Global Andrology Forum.

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Osvaldo Rajmil[136], Dung Mai Ba Tien[31], Yiming Yuan[44], Juan Francisco Lizarraga-Salas[137], Balantine Eze[138], Kay Seong Ngoo[139], Joe Lee[140], Umut Arslan[12], Ashok Agarwal[122,141]; Global Andrology Forum*

[1]*Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy,* [2]*Glickman Urological & Kidney Institute, Cleveland Clinic Foundation, Cleveland, OH, USA,* [3]*Department of Urology, Lilavati Hospital and Research Centre, Mumbai, India,* [4]*Department of Urology, King Abdulaziz University, Jeddah, Saudi Arabia,* [5]*Department of Urology, Faculty of Medicine, Minia University, Minia, Egypt,* [6]*Department of Reproductive Biology, Fertility Preservation, Andrology, CECOS, Poissy Hospital, Poissy,* [7]*Department of Biology, Reproduction, Epigenetics, Environment and Development, Paris Saclay University, UVSQ, INRAE, BREED, Jouy-en-Josas, France,* [8]*Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt,* [9]*Department of Urology, Selçuk University School of Medicine, Konya, Turkey,* [10]*Department of Urology, Henry Ford Health System, Vattikuti Urology Institute, Detroit, MI,* [11]*Department of Reproductive Urology, Austin Fertility & Reproductive Medicine/Westlake IVF, Austin, TX, USA,* [12]*Department of Urology, Fatih Sultan Mehmet Training and Research Hospital, University of Health Sciences, Istanbul, Turkey,* [13]*Urology and Nephrology Center, Mansoura University, Mansoura, Egypt,* [14]*Department of Surgery, Urology Unit, Farwaniya Hospital, Farwaniya,* [15]*Department of Urology, Sabah Al Ahmad Urology Center, Kuwait City, Kuwait,* [16]*Department of Urology, Loma Linda University Health, Loma Linda, CA, USA,* [17]*Department of Urology, Başakşehir Çam and Sakura City Hospital, Istanbul, Turkey,* [18]*Department of Physiology, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, Malaysia,* [19]*Department of Internal Medicine, Trinity Health/Mercy Health, Muskegon, MI, USA,* [20]*Department of Urology, Reproduction Center, Yokohama City University Medical Center, Yokohama, Japan,* [21]*Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK,* [22]*Department of Medical Bioscience, University of the Western Cape, Bellville, South Africa,* [23]*Department of Endocrinology, Polytechnic University of Marche, Ancona, Italy,* [24]*Reproductive Medicine, Clinical Research Centre, Lund University, Malmö, Sweden,* [25]*Fetal Health Research Center, Hope Generation Foundation, Tehran,* [26]*Gene Therapy and Regenerative Medicine Research Center, Hope Generation Foundation, Tehran, Iran,* [27]*Department of Urology, Molinette Hospital, A.O.U. Città della Salute e della Scienza, University of Turin, Torino, Italy,* [28]*IVIRMA Global Research Alliance, IVI Foundation, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain,* [29]*Department of Urology, Andrology and Renal Transplant, AIG Hospitals, Hyderabad, India,* [30]*Department of Molecular Cell and Cancer Biology, University of Massachusetts Medical School, Worcester, MA, USA,* [31]*Department of Andrology, Binh Dan Hospital, Ho Chi Minh,* [32]*Department of Urology and Andrology, Pham Ngoc Thach University of Medicine, Ho Chi Minh, Vietnam,* [33]*Department of Urology, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia,* [34]*Andrology and IVF Center, Next Fertility Procrea, Lugano, Switzerland,* [35]*Department of Urology, Istanbul Medipol Mega University Hospital, Istanbul, Turkey,* [36]*Department of Urology, Innsbruck Medical University, Innsbruck, Austria,* [37]*Center for Andrology and Sexual Medicine, Viet Duc University Hospital, Hanoi,* [38]*Department of Urology, Andrology and Sexual Medicine, University of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam,* [39]*Division of Urology, Department of Surgery, McGill University, Montreal, QC, Canada,* [40]*Department of Andrology, Sexology & STIs, Faculty of Medicine, Cairo University, Cairo, Egypt,* [41]*Central Drug Research Institute, Male Reproductive Health Research Laboratory, Lucknow, Uttar Pradesh,* [42]*Division of Endocrinology, Central Drug Research Institute, Lucknow, India,* [43]*Division of Urology, Centro Universitário FMABC, Santo André, Brazil,* [44]*Department of Urology, Peking University Third Hospital, Peking University, Beijing, China,* [45]*Department of Urology, University Hospital of Rostock, Rostock, Germany,* [46]*American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA,* [47]*Department of Urology, Hamad Medical Corporation, Doha,* [48]*Department of Urology, Weill Cornell Medical-Qatar, Doha, Qatar,* [49]*Department of Urology, Aristotle University School of Medicine, Thessaloniki, Greece,* [50]*Department of Urology, Topiwala National Medical College, B.Y.L Nair Ch Hospital, Mumbai,* [51]*Andrology Unit, Department of Urology, Apollo Hospitals, Greams Road, Chennai, India,* [52]*Department of Urology, Kobe University Graduate School of Medicine, Kobe, Japan,* [53]*Department of Urology, Istanbul Faculty of Medicine, Istanbul University, Istanbul,* [54]*Department of Urology, Ege University, Izmir,* [55]*Urocentre Urology Clinic, Adana, Turkey,* [56]*Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania,* [57]*Department of Urology, Faculty of Medicine, Hatay Mustafa Kemal University, Antakya, Hatay, Turkey,* [58]*Department of Urology, Astghik Medical Center, Yerevan, Armenia,* [59]*Men's Health Melbourne, Victoria,* [60]*Department of Surgery, Western Precinct, University of Melbourne, Victoria,* [61]*Department of Urology, Western Health, Victoria,* [62]*Department of Urology, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia,* [63]*Fleury Group and Hospital Israelita Albert Einstein, São Paulo,* [64]*Department of Clinical Surgery, Health Sciences Sector of the Federal University of Parana (UFPR), Curitiba, Paraná, Brazil,* [65]*Department of Urology, Ioannina University School of Medicine, Ioannina,* [66]*2nd Department of Urology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece,* [67]*SCM Clinic and Hospital, New Delhi, India,* [68]*Division of Urology, Department of Surgery, Prof. Dr. Sardjito Hospital, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta,* [69]*Department of Urology, Hasan Sadikin Hospital, Medical Faculty of Padjadjaran University, Bandung, Indonesia,* [70]*Department of Urology, Juntendo University Urayasu Hospital, Chiba,* [71]*Department of Urology, Nagano Red Cross Hospital, Nagano, Japan,* [72]*Department of Urology, College of Medicine and Pharmacy, Ibn Zohr University, Agadir, Morocco,* [73]*Elang Medika Corpora Hospital, Tangerang, Indonesia,* [74]*Section of Urology, Department of Surgery, University of Santo Tomas Hospital, Manila, Philippines,* [75]*Department of Urology, Pusan National University School of Medicine, Busan,* [76]*Medical Research Institute of Pusan National University Hospital, Busan, Korea,* [77]*SENSART Clinic, Istanbul,* [78]*Department of Urology, Baskent University Faculty of Medicine, Ankara,* [79]*Department of Urology, Ankara University School of Medicine, Ankara, Turkey,* [80]*Department of Andrology, Hammersmith Hospital, Imperial, London,* [81]*Department of Urology, Imperial Healthcare NHS Trust, Charing Cross Hospital, London, UK,* [82]*Department of Urology, Burjeel Hospital, Abu Dhabi,* [83]*Clinical Urology, College of Medicine and Health Sciences, Khalifa University, Abu Dhabi, UAE,* [84]*Institute of Urology, University Hospitals, Case Western Reserve University, Cleveland, OH,* [85]*Division of Urology, Southern Illinois University School of Medicine, Springfield, IL,* [86]*Department of Urology, College of Medicine and Life Sciences, University of Toledo, Toledo, OH, USA,* [87]*Department of Surgery, School of Medicine, Taylor's University, Subang Jaya, Selangor, Malaysia,* [88]*Instituto de Ginecología y Fertilidad (IFER) y Universidad Barcelo, Buenos Aires, Argentina,* [89]*AndroOne Men's Health Clinic, Salem,* [90]*Department of Physiology, All India Institute of Medical Sciences Mangalagiri, Mangalagiri, India,* [91]*Department of Urology, Dr Wahidin Sudirohusodo Hospital, Makassar, Indonesia,* [92]*Division of Urology, Department of Surgery, Faculty of Medicine, King*

*Saud University, Riyadh, Saudi Arabia, [93]Department of Urology, Biruni University School of Medicine, Istanbul, Turkey, [94]Department of Urology, Western General Hospital, Edinburgh, UK, [95]Urology Department, University of Texas McGovern Medical School, Houston, TX, [96]Department of Urology, MD Anderson Cancer Center, Houston, TX, USA, [97]Department of Urology, Dr. Dradjat Hospital, Serang, Indonesia, [98]Department of Andrology and Sexual Medicine, Hanoi Medical University's Hospital, Hanoi, Vietnam, [99]Clarity Health, Chandigarh, India, [100]Andrology Department at Ideia Fértil Institute, Santo André, São Paulo, Brazil, [101]Department of Urology and Andrology, Locus Medicus, Athens, Greece, [102]Department of Urology, Sawai Man Singh Medical College and Hospital, Jaipur, Rajasthan, India, [103]Department of Urology, Prof. Dr. I.G.N.G Ngoerah General Hospital, Faculty of Medicine, Universitas Udayana, Bali, Indonesia, [104]Department of Andrology & Reproductive Medicine, Jindal Hospital & Fertility Center, Meerut, India, [105]Department of Urology, Prof R.D. Kandou Hospital, Manado, Indonesia, [106]Urology Department, Tehran University of Medical Scienes, Tehran, Iran, [107]Department of Urology, University of Illinois at Chicago, Chicago, IL, USA, [108]Department of Urology and Renal Transplantation, Univeristy of Foggia, Foggia, Italy, [109]Department of Urology, Lebanese University, Beirut, Lebanon, [110]Department of Urology, Military Teaching Hospital, Rabat, Morocco, [111]Department of Surgery, Urology Division, Sultan Qaboos University, Muscat, Oman, [112]Urology Clinic, Moscow, Russia, [113]Department of Urology, Dr. George Mukhari Academic Hospital, Sefako Makgatho Health Science University, Medunsa, Ga-Rankuwa, South Africa, [114]Department of Urology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea, [115]Department of Obstetrics and Gynecology, University of Health Sciences, Kanuni Training and Research Hospital, Trabzon, Turkey, [116]Department of Urology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [117]Department of Anatomy, Faculty of Medicine, Faculty Tunis Manar, Tunis, Tunisia, [118]Department of Urology, Gülhane Research and Training Hospital, University of Health Sciences, Ankara, Turkey, [119]Fakih IVF Fertility Center, Abu Dhabi, UAE, [120]Department of Urology, Oxford University Hospital, Oxford, UK, [121]Global Andrology Forum, Moreland Hills, OH, USA, [122]Department of Urology, School of Medicine and Health Sciences, University of Lusaka, Lusaka, Zambia, [123]Sexual Health and Fertility Research Center, Shahroud University of Medical Sciences, Shahroud, Iran, [124]IVF Jakarta - YPK Mandiri, Jakarta, Indonesia, [125]Tam Anh IVF Center, Tam Anh General Hospital, Hanoi, [126]Department of Obstetrics and Gynecology, Hanoi Obstetric and Gynecology Hospital, Hanoi, Vietnam, [127]Department of Urology, Soetomo Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, [128]Department of Urology, Universitas Airlangga Teaching Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, [129]Department of Urology, General Hospital, Cuprija, Serbia, [130]Department of Reproduction and Artificial Insemination, Faculty of Veterinary Medicine, Kafkas University, Kars, Turkey, [131]FertilTree-Jaslok International Fertility Centre, Jaslok Hospital, Mumbai, Maharashtra, [132]Cure & SK Hospital, Trivandrum, India, [133]Department of Anatomy, Khesar Gyalpo University of Medical Sciences of Bhutan, Thimphu, Bhutan, [134]Andrology Study Program, Department of Biomedical Sciences, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, [135]Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Sumedang, West Java, Indonesia, [136]Department of Andrology, Fundacio Puigvert, Barcelona, Spain, [137]Instituto de Ciencias en Reproducción Humana Vida, León, Mexico, [138]Department of Surgery, College of Medicine, Enugu State University of Science and Technology, Enugu, Nigeria, [139]Urology Unit, Department of Surgery, Hospital Angkatan Tentera Tuanku Mizan, Kuala Lumpur, Malaysia, [140]Department of Urology, National University Hospital, Singapore, [141]Cleveland Clinic, Cleveland, OH, USA*

**Purpose:** The purpose of this meta-analysis is to study the impact of varicocele repair in the largest cohort of infertile males with clinical varicocele by including all available studies, with no language restrictions, comparing intra-person conventional semen parameters before and after the repair of varicoceles.

**Materials and Methods:** The meta-analysis was performed according to PRISMA-P and MOOSE guidelines. A systematic search was performed in Scopus, PubMed, Cochrane, and Embase databases. Eligible studies were selected according to the PICOS model (Population: infertile male patients with clinical varicocele; Intervention: varicocele repair; Comparison: intra-person before-after varicocele repair; Outcome: conventional semen parameters; Study type: randomized controlled trials [RCTs], observational and case-control studies).

**Results:** Out of 1,632 screened abstracts, 351 articles (23 RCTs, 292 observational, and 36 case-control studies) were included in the quantitative analysis. The before-and-after analysis showed significant improvements in all semen parameters after varicocele repair (except sperm vitality); semen volume: standardized mean difference (SMD) 0.203, 95% CI: 0.129–0.278; p<0.001; I2=83.62%, Egger's p=0.3329; sperm concentration: SMD 1.590, 95% CI: 1.474–1.706; p<0.001; I2=97.86%, Egger's p<0.0001; total sperm count: SMD 1.824, 95% CI: 1.526–2.121; p<0.001; I2=97.88%, Egger's p=0.0063; total motile sperm count: SMD 1.643, 95% CI: 1.318–1.968; p<0.001; I2=98.65%, Egger's p=0.0003; progressive sperm motility: SMD 1.845, 95% CI: 1.537%–2.153%; p<0.001; I2=98.97%, Egger's p<0.0001; total sperm motility: SMD 1.613, 95% CI 1.467%–1.759%; p<0.001; I2=97.98%, Egger's p<0.001; sperm morphology: SMD 1.066, 95% CI 0.992%–1.211%; p<0.001; I2=97.87%, Egger's p=0.1864.

**Conclusions:** The current meta-analysis is the largest to date using paired analysis on varicocele patients. In the current meta-analysis, almost all conventional semen parameters improved significantly following varicocele repair in infertile patients with clinical varicocele.

**Keywords:** Controlled before-after studies; Infertility, male; Meta-analysis; Varicocele

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## INTRODUCTION

Varicocele is a condition defined as abnormal dilatation and tortuosity of the pampiniform plexus of veins in the scrotum and spermatic cord [1]. The condition is common with a variable reported prevalence, depending on the method of varicocele identification, the person's age, and the fertility status. Among the general male population, a clinical (palpable) varicocele is reported in 15% to 18% of male subjects, while a varicocele is detectable in 35% of male subjects during color duplex ultrasonography examination [2]. A higher prevalence is reported among infertile male subjects, with 35% of male with primary infertility and 81% of male with secondary infertility having clinical varicoceles [3]. Although left-side clinical varicoceles are more common, in up to 50% of the cases the varicoceles are bilateral, though the left-side varicoceles are almost always larger than the right-side varicoceles [1].

The association between male infertility and varicoceles has been widely studied over the past several decades. In a large study conducted by World Health Organization (WHO), which included 9,038 male from 34 centers over 12 months, 25% of the male with abnormal semen analysis had a varicocele [4]. However, the precise etiology and pathogenesis of varicocele are still elusive. Several mechanisms have been postulated to explain the development of varicoceles in males [5]. However, the mechanisms by which varicocele affects male fertility and, similarly, whether varicocelectomy is beneficial or not, are not fully understood. Oxidative stress, heat stress, local hormonal imbalances, testicular hypoperfusion, and stasis of blood with an accumulation of toxins have all been suggested as potential mechanisms through which varicocele may negatively impact male reproductive health. Nevertheless, none of these mechanisms can stand alone to precisely explain the deleterious effects of varicoceles on testicular function [6].

Current guidelines from the European Association of Urology (EAU) and the American Urologic Association and the American Society of Reproductive Medicine (AUA/ASRM) recommend varicocele repair for a man with a palpable varicocele, infertility, one or more semen abnormalities, and a normally fertile female partner [7,8]. EAU guidelines also state that "varicocele repair may lead to sperm appearing in the ejaculate in male with non-obstructive azoospermia." Despite the guidelines' recommendations, the association between male infertility and varicoceles is still unclear. Although varicoceles are referred to as the most surgically correctable cause of male infertility [9] a recent Cochrane Systematic Review concluded that it is uncertain whether varicocele repair compared to no treatment in subfertile men led to an improvement in live birth rates, as the quality of evidence was considered poor [10]. Further, many men who have a varicocele have successfully fathered children naturally without any treatment. There are also discrepancies between the AUA and EAU male infertility guidelines regarding which patients may benefit from varicocele repair [7,8]. Systematic reviews and meta-analyses have previously been performed evaluating the role of varicocele repair in male infertility; however, these have been limited by English language articles leading to analysis of relatively small sample sizes [11,12]. A meta-analysis on a very large sample size of infertile male with varicoceles who underwent varicocele repair is needed to clarify the association between varicocele repair and improvement in semen parameters. The latter represent valuable outcomes to measure the effect of varicocele repair on male infertility since semen parameters reflect men's health and testicular function, while pregnancy or live birth is multifactorial, depending on a multitude of factors, including female fertility status.

Accordingly, the objective of this study is to assess the impact of varicocele repair on conventional semen parameters by comparing values before and after repair in infertile male.

## MATERIALS AND METHODS

### 1. Search strategy

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) for RCTs [13,14], and the MOOSE guidelines for Meta-analyses and Systematic Reviews of Observational Studies [15]. The search strategy comprised a combination of the following Medical Subjects Headings (MeSH) and search terms: varicoc*, management, embolization/embolisation, microsurg*/micro-surg*, varicocelectomy, repair, correction, treatment, ligation, surg*, operation, radiolog*, sperm*, semen, seminal, ejaculate, asperm*/azoo*/azoosperm*, oligo*/oligosperm*/oligozoosperm*,

astheno*/asthenosperm*/asthenozoosperm*, terato*/teratosperm*/teratozoosperm*, and necro*/necrosperm*/necrozoosperm*. These exhaustive systematic searches were performed in the Scopus, PubMed, Cochrane, and Embase databases, between 1970 to the present. While the search was limited to only original articles and human studies, there were no language restrictions applied. After the elimination of duplicates, the abstracts identified by the searches were screened for eligibility. For each article, an assessment of eligibility was performed by two independent reviewers in an unblinded manner. The titles and abstracts of the studies were first independently screened for inclusion. In cases of uncertainty, each researcher screened the full text to determine inclusion. Any disagreements between reviewers were resolved by discussion between the two reviewers. However, if no consensus was reached, then a third reviewer made the final decision.

Full papers of the eligible abstracts were downloaded, including non-English papers which were translated into English by native speakers of the language of the article. The full papers were assessed for eligibility using the PICOS (Population, Intervention, Comparison/Comparator, Outcome, Study type) model question (Table 1) [16], and the selected papers were subjected to data extraction. The selection of eligible studies and data extraction was performed by a group of 37 researchers. Prior to assessing the studies, these researchers underwent methodical training exercises to ensure that a standardized approach was applied throughout the study [17]. The protocol of this systematic review and meta-analysis was registered with PROSPERO (number CRD42022329848).

## 2. Data extraction

The following data were collected: study design, characteristics of varicocele and varicocele repair (method, laterality), time from varicocele repair to first follow-up evaluation, number of patients, various semen parameters (semen volume, sperm concentration, total sperm count, total motile sperm count, progressive sperm motility, total sperm motility, sperm vitality, and sperm morphology) before and after varicocele repair.

## 3. Quality assessment

The quality of evidence (QoE) of the studies was assessed at the same time as data extraction, by a team of thirty-seven researchers supervised by twelve team leaders and co-team leaders.

All studies were assessed using the Cambridge Quality Checklists [18]. Further assessment of QoE was performed for randomized controlled trials (RCTs) using three other scales specific to this study design: the Cochrane Risk of Bias [19], the Jadad score [20], and the CONSORT guidelines [21]. The last three scales were used to allow for better stratification and evaluation of the QoE of each study with a wider range of scores resulting from the sum of the different scales.

The selection of eligible studies, data extraction, and QoE assessment was performed by a group of 37 researchers, as detailed elsewhere [17,22].

## 4. Statistical analysis

The statistical analysis was performed using MedCalc Statistical Software (version 20.027; MedCalc Software Ltd). Standardized mean difference (SMD) between pre- and post-varicocelectomy with standard error and 95% confidence interval (95% CI) were used

**Table 1.** PICOS model (population, intervention, comparison/comparator, outcomes, study type)

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | Infertile male with clinical varicocele | Adolescents |
| Intervention | Varicocele repair | - |
| Comparison | i) Conventional semen parameters analyzed before varicocele repair.<br>ii) Conventional semen parameters analyzed after varicocele repair. | - |
| Outcome | Conventional semen parameters: semen volume, sperm concentration, total sperm count, total motile sperm count, progressive sperm motility, total sperm motility, sperm vitality, and sperm morphology | - |
| Study type | Randomized controlled studies, observational studies | Animal studies, *In vitro* studies, Reviews and Meta-analyses, Case reports, Book chapters, Editorials |

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to evaluate the outcomes and calculated according to both the fixed and random effects models based on the level of in-between study heterogeneity [23]. Heterogeneity between the different studies was determined using the Cochrane's Q-test and $I^2$ statistic for inconsistency [24] with an $I^2$ value higher than 50% indicating inconsistency among the studies analyzed. The random-effect model was chosen if significant heterogeneity was detected, while the fixed-effect model was chosen if no significant heterogeneity was detected. Possible publication bias was evaluated using Egger's test [25]. Results are presented as Forest plots. For all tests employed a p-value<0.05 was considered significant.

## RESULTS

One thousand six hundred and thirty-two abstracts were extracted using the above-mentioned search strategy. After removing 661 duplicates, 971 abstracts were evaluated. Of these, 100 articles were identified by title and abstract as reviews, case reports, book chapters, or as papers on unrelated topics and were therefore excluded. Of the remaining 871 articles, 164 full-texts were not found, whereas 154 were excluded after reading the full-text because they had no extractable data (*e.g.*, data reported as median and interquartile range), and 200 were excluded because of different outcomes. Finally, 351 studies assessing the impact of varicocele repair on conventional semen parameters using a before-after approach were included in the present analysis (Fig. 1).

Among the 351 included studies, 292 were observational and 36 were case-control studies. The remaining 23 studies were RCTs. The main characteristics of the included studies are shown in Table 2 [26-367]. QoE assessment is provided in Table 3 and 4 [26-366].

### 1. Semen volume

The result of the before-after analysis of semen volume is summarized in Table 5.

Eighty-two articles were included to analyze this outcome, for a total of 12,566 infertile patients with clinical varicocele before varicocele repair, and 10,825 patients after varicocele repair. The analysis of combined results showed a significantly higher semen volume in patients following varicocele repair compared to the

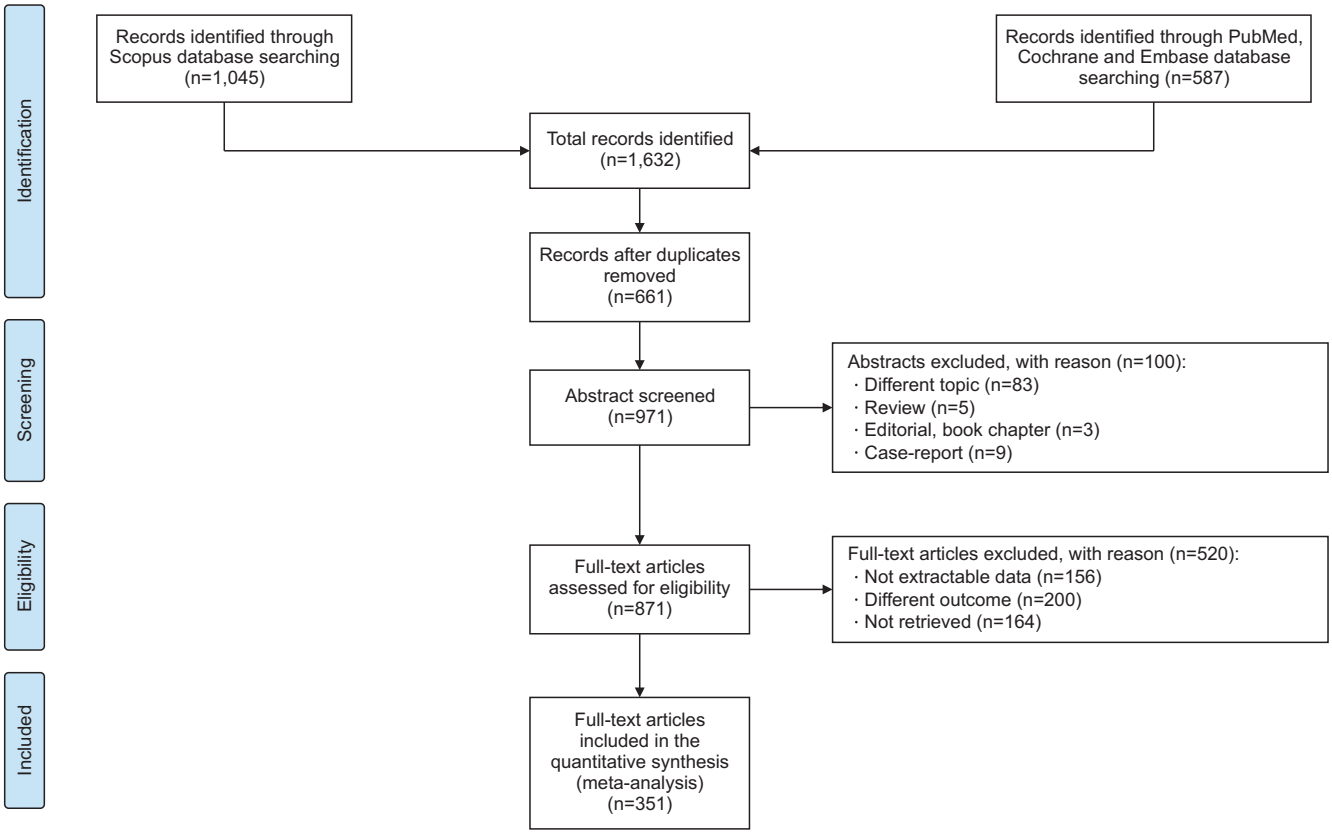


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart

**Table 2.** Endpoint measures of the included studies

| First author | Year | Study design | Outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Haensch [26] | 1976 | Observational | X | X | | | | | | X |
| Rodriguez-Rigau [27] | 1978 | Observational | X | X | | | X | | X | |
| Johnsen [28] | 1978 | Observational | | | X | | | | | X |
| Nilsson [29] | 1979 | Observational | X | X | X | | X | | | X |
| Greenberg [30] | 1979 | Observational | X | X | | X | | | | X |
| Homonnai [31] | 1980 | Observational | | X | | X | | | | X |
| Gogol [32] | 1980 | Observational | | X | | | | | | X |
| Lukkarinen [33] | 1984 | Observational | X | X | | | X | | | X |
| Foresta [34] | 1984 | Observational | | X | | | X | | | |
| Tinga [35] | 1984 | Observational | | | X | | X | | | X |
| Shinoda [36] | 1985 | Observational | X | X | | | X | | | |
| Marmar [37] | 1985 | Observational | | X | | | X | | | X |
| Segenreich [38] | 1986 | Observational | | X | | | | | | |
| Vereecken [39] | 1986 | Observational | | X | | | X | | | X |
| Hadziselimovic [40] | 1986 | Observational | X | X | | | X | | | X |
| Burke [41] | 1987 | Observational | | | | | X | | | X |
| Nagai [42] | 1988 | Observational | | | X | | X | | | |
| Okuyama [43] | 1988 | Observational | | X | | | | X | | |
| Gerris [44] | 1988 | Observational | | X | | | X | | | |
| Yarborough [45] | 1989 | Observational | | X | | | X | | | X |
| Parsch [46] | 1990 | Observational | | X | X | | X | X | X | X |
| Kuroiwa [47] | 1991 | Observational | X | X | | | X | | | |
| Dhabuwala [48] | 1992 | Observational | | X | | | | X | | X |
| Donovanjr [49] | 1992 | Observational | | X | | | X | | X | |
| Ito [50] | 1993 | Observational | X | X | | | X | | | |
| Steckel [51] | 1993 | Observational | | X | | | X | | | |
| Ross [52] | 1993 | Observational | | X | | | X | | | X |
| Hirokawa [53] | 1993 | Observational | | X | | | | | X | |
| Lerchl [54] | 1993 | Observational | | X | X | | X | | | X |
| Kondoh [55] | 1993 | Observational | | X | | | X | | | |
| Yamamoto [56] | 1994 | Observational | | X | | | | X | | X |
| Dewire [57] | 1994 | Observational | | X | | | X | | | |
| Knudson [58] | 1994 | Observational | | X | | | X | | X | |
| Nakada [59] | 1994 | Observational | | X | | | X | | | |
| Yamamoto [60] | 1995 | Observational | | X | | | | X | | X |
| Ferguson [61] | 1995 | Observational | X | X | | | X | | | X |
| Chiang [62] | 1995 | Observational | | X | | | X | | | |
| Segenreich [63] | 1995 | Observational | | X | X | | | | | |
| Watanabe [64] | 1995 | Observational | | X | | | | | | |
| Su [65] | 1995 | Observational | | X | | | X | | | |
| Parikh [66] | 1996 | Observational | | | X | | X | X | | |
| Jarow [67] | 1996 | Observational | | | X | | | | | |
| Punekar [68] | 1996 | Observational | | | X | | X | | | |
| Takahara [69] | 1996 | Observational | | X | | | X | | | |
| Atikeler [70] | 1996 | Observational | | X | | | X | | | |
| Vazquez-Levin [71] | 1997 | Observational | X | X | X | | X | | | X |
| Segenreich [72] | 1997 | Observational | | X | X | | | | | |

Table 2. Continued 1

| First author | Year | Study design | Outcome | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Seftel [73] | 1997 | Observational | | X | | | X | | | X |
| Hauser [74] | 1997 | Observational | | X | | | X | | | |
| Bablok [75] | 1997 | Observational | | X | | | X | | | |
| Nozawa [76] | 1997 | Observational | | X | | | | X | | X |
| Johnsen [77] | 1997 | Observational | | X | | | | X | | |
| Flati [78] | 1997 | Observational | | X | | | X | | | |
| Barbalias [79] | 1998 | Observational | | X | | | X | | | X |
| Abdulmaaboud [80] | 1998 | Observational | | X | | | X | | | X |
| Aşci [81] | 1998 | Observational | | X | | | | X | | X |
| Matthews [82] | 1998 | Observational | | | | | | | X | |
| Schatte [83] | 1998 | Observational | X | X | | | X | X | X | X |
| Madjar [84] | 1998 | Observational | | | X | | X | | | X |
| Ismail [85] | 1999 | Observational | X | X | | | X | X | | |
| Zini [86] | 1999 | Observational | | X | | | X | | | X |
| Kim [87] | 1999 | Observational | | | X | | X | | | |
| Scherr [88] | 1999 | Observational | | X | X | | X | | X | X |
| Uygur [89] | 1999 | Observational | | | X | | X | | | X |
| Chiang [90] | 1999 | Observational | | X | | | X | | | X |
| Reichart [91] | 2000 | Observational | X | | X | | X | X | | X |
| Grasso [92] | 2000 | Observational | | X | | | | X | | X |
| Pianalto [93] | 2000 | Observational | | X | | | X | | | X |
| Cayan [94] | 2000 | Observational | | X | | | X | | | |
| Papanikolaou [95] | 2000 | Observational | | X | | | X | | X | |
| Pierik [96] | 1998 | Observational | | X | | | X | | | X |
| Kamal [97] | 2001 | Observational | | X | | | X | | X | |
| Cayan [98] | 2001 | Observational | | | | | | | X | |
| Mostafa [99] | 2001 | Observational | | X | | | | | | |
| Jungwirth [100] | 2001 | Observational | | X | | | | X | | |
| Cavallaro [101] | 2001 | Observational | | X | | | X | | | X |
| Avila-Vergara [102] | 2001 | Observational | | X | | X | X | | | |
| Cayan [103] | 2002 | Observational | | | | | | | | X |
| Kibar [104] | 2002 | Observational | X | X | | | X | | | X |
| Onozawa [105] | 2002 | Observational | | X | | | X | | | X |
| Iwasaki [106] | 2003 | Observational | X | X | | | X | | | |
| Hsieh [107] | 2003 | Observational | | X | | | X | | | X |
| Younes [108] | 2003 | Observational | X | | X | | | | | |
| Fuse [109] | 2003 | Observational | | X | | | X | | X | |
| Nuhoğlu [110] | 2004 | Observational | | X | | | | X | | X |
| Ishikawa [111] | 2004 | Observational | | X | | | X | | | |
| O'Brien [112] | 2004 | Observational | | X | | | X | | | |
| Polito [113] | 2004 | Observational | | X | | | | X | | |
| Flati [114] | 2004 | Observational | X | X | | | X | | | |
| Grober [115] | 2004 | Observational | X | X | | | X | | X | X |
| Grober [116] | 2004 | Observational | | | | | X | | X | |
| Gat [117] | 2004 | Observational | | X | | | X | | | X |
| Gat [118] | 2004 | Observational | | X | | | X | | | X |
| Gat [119] | 2004 | Observational | | X | | | X | | | X |

Table 2. Continued 2

| First author | Year | Study design | Outcome | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Ortapamuk [120] | 2005 | Observational | | X | | | X | | | |
| Ketabchi [121] | 2005 | Observational | | X | | | X | | | X |
| Watanabe [122] | 2005 | Observational | | X | | | X | | | |
| Nasr-Esfahani [123] | 2005 | Observational | | X | X | | X | | | X |
| Yeşilli [124] | 2005 | Observational | | X | | | X | | | X |
| Mancini [125] | 2005 | Observational | | X | | | X | | | |
| Pasqualotto [126] | 2005 | Observational | | X | | | X | | | |
| Ishikawa [127] | 2005 | Observational | | X | | | X | | | |
| Zini [128] | 2005 | Observational | | X | | | X | | | X |
| Benoff [129] | 2005 | Observational | | X | | | | | | |
| Pasqualotto [130] | 2005 | Observational | | X | | | X | | | |
| Ku [131] | 2005 | Observational | | X | | | X | | | X |
| Pasqualotto [132] | 2005 | Observational | | X | | | X | | | |
| Mehrsai [133] | 2005 | Observational | | X | | | X | | | X |
| Orhan [134] | 2005 | Observational | | X | | | X | | | X |
| Libman [135] | 2006 | Observational | X | X | | | X | | | X |
| Ramasamy [136] | 2006 | Observational | | | | | | | X | |
| Hussein [137] | 2006 | Observational | | X | | | X | | | X |
| Zucchi [138] | 2006 | Observational | | X | | | | X | | |
| Hsieh [139] | 2006 | Observational | | X | | | X | | | |
| Baccetti [140] | 2006 | Observational | | X | | | X | X | | |
| Djaladat [141] | 2006 | Observational | | X | | | X | | | |
| Shin [142] | 2006 | Observational | | X | | | X | | | |
| Ashrafi [143] | 2007 | Observational | | X | X | | X | | | X |
| Okeke [144] | 2007 | Observational | X | X | | X | X | | | X |
| Qadan [145] | 2007 | Observational | | X | | | | | | |
| Zini [146] | 2008 | Observational | X | X | | | X | | X | X |
| Ozden [147] | 2008 | Observational | | X | | | | X | | X |
| Flacke [148] | 2008 | Observational | | X | | | X | | | X |
| Al-Said [149] | 2008 | Observational | | X | | | X | | | |
| Atalay [150] | 2008 | Observational | X | X | | | | X | | X |
| Cakan [151] | 2008 | Observational | X | X | | | X | | | X |
| Balci [152] | 2008 | Observational | | X | | | X | | X | X |
| Gandini [153] | 2008 | Observational | | X | | | X | | | X |
| Chen [154] | 2008 | Observational | | | | | X | | | X |
| Agnifili [155] | 2008 | Observational | | X | | | | | X | |
| Juárez-Albarrán [156] | 2008 | Observational | | X | | | | | | |
| Kadhim [157] | 2009 | Observational | | X | | | | X | | |
| Elbendary [158] | 2009 | Observational | X | X | | | X | X | X | |
| Shamsa [159] | 2009 | Observational | | X | | | X | | | X |
| Hafez [160] | 2009 | Observational | | X | | | X | | | X |
| Salem [161] | 2009 | Observational | | X | | | X | | | |
| Jasemi [162] | 2009 | Observational | | X | | | | X | | |
| Zheng [163] | 2009 | Observational | | X | | | X | | | X |
| Nasr-Esfahani [164] | 2009 | Observational | | X | X | | X | | | X |
| Zorba [165] | 2009 | Observational | | | | | | | X | |
| Kondo [166] | 2009 | Observational | | X | | | X | | | |

Table 2. Continued 3

| First author | Year | Study design | Outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Acar [167] | 2009 | Observational | X | X | | | | X | | X |
| Fall [168] | 2010 | Observational | | X | | | X | | | X |
| Al-Adl [169] | 2010 | Observational | X | X | | | X | | X | |
| Abdelwahab [170] | 2010 | Observational | | X | | | X | | | X |
| Li [171] | 2010 | Observational | X | X | | X | | X | | |
| Dadfar [172] | 2010 | Observational | | | X | | X | | | X |
| Al-Ghazo [173] | 2011 | Observational | | | | | | | X | |
| Azadi [174] | 2011 | Observational | | X | | | X | | | X |
| Abd Ellatif [175] | 2011 | Observational | | X | | | X | | | X |
| Giagulli [176] | 2011 | Observational | | X | | | X | | | X |
| Cho [177] | 2011 | Observational | | X | X | | | X | X | X |
| Chen [178] | 2011 | Observational | X | X | | | X | | | X |
| Zini [179] | 2011 | Observational | | X | | | | X | | |
| Hsiao [180] | 2011 | Observational | | X | X | | X | X | | X |
| Ghazi [181] | 2011 | Observational | X | X | | | X | X | | X |
| Tarhan [182] | 2011 | Observational | | X | | | X | | X | X |
| Ozturk [183] | 2012 | Observational | | X | | | X | | | X |
| Mohamid [184] | 2012 | Observational | | X | | | X | | | X |
| Shiraishi [185] | 2012 | Observational | X | X | | | | | X | |
| Li [186] | 2012 | Observational | | X | | | | X | | |
| Tavalaee [187] | 2012 | Observational | | | X | | X | | | X |
| Pirinççi [188] | 2012 | Observational | | X | | | | | | X |
| Gabriel [189] | 2012 | Observational | | X | | | X | | | |
| Mehraban [190] | 2012 | Observational | | X | | | | | | |
| El-Haggar [191] | 2012 | Observational | | X | | | | | | |
| La Vignera [192] | 2012 | Observational | X | X | X | X | | X | | X |
| Ozturk [183] | 2012 | Observational | | X | | | | | | X |
| Navaeian-Kalat [193] | 2012 | Observational | | X | | | | | | |
| Armağan [194] | 2012 | Observational | | X | | | X | | | |
| Kim [195] | 2012 | Observational | X | X | | | | | | X |
| Keyhan [196] | 2012 | Observational | | | X | | | | | X |
| Abdelrahman [197] | 2012 | Observational | | X | | | | | | |
| Al Bakri [198] | 2012 | Observational | X | X | | | X | | X | X |
| Lee [199] | 2011 | Observational | | X | | | | | | X |
| Sun [200] | 2012 | Observational | | X | | | | | | X |
| Ollandini [201] | 2013 | Observational | | X | | | | X | | |
| Leung [202] | 2013 | Observational | | X | | | | | | X |
| Bonyadi [203] | 2013 | Observational | X | X | | | | | | |
| Smit [204] | 2013 | Observational | | X | X | | | X | | X |
| Camargo [205] | 2013 | Observational | X | X | | | | X | | X |
| Zhang [206] | 2014 | Observational | | X | | | X | | X | X |
| Kang [207] | 2013 | Observational | | X | | | X | | | X |
| Bozhedomov [208] | 2014 | Observational | X | X | | | | X | | |
| Camargo [209] | 2014 | Observational | X | X | | | X | | | X |
| Prasivoravong [210] | 2014 | Observational | | | X | X | | X | | X |
| Komiya [211] | 2014 | Observational | X | X | | | | | | X |
| Wang [212] | 2014 | Observational | | X | | | | X | | X |

Table 2. Continued 4

| First author | Year | Study design | Outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Enatsu [213] | 2014 | Observational | | X | | | X | | | |
| Samplaski [214] | 2014 | Observational | X | X | | | | | X | X |
| Hosseinifar [215] | 2014 | Observational | X | X | | | X | | | X |
| Kadioglu [216] | 2014 | Observational | X | X | | | | X | | |
| Lehtihet [217] | 2014 | Observational | X | | X | | X | X | | |
| Al-Adl [218] | 2014 | Observational | X | X | | | X | | X | |
| Li [219] | 2014 | Observational | | X | | | | | | |
| Chen [220] | 2014 | Observational | | X | | | X | | | X |
| Lee [221] | 2014 | Observational | | X | | | X | | | |
| Choe [222] | 2015 | Observational | X | X | | | X | | | X |
| Guo [223] | 2015 | Observational | | X | | | X | X | | X |
| Kiziler [224] | 2015 | Observational | | X | | | X | | | |
| Zhang [225] | 2015 | Observational | | X | | | | | | |
| Youssef [226] | 2015 | Observational | | X | | | | | | X |
| Cantoro [227] | 2015 | Observational | | X | | | X | | | |
| Ener [228] | 2015 | Observational | | X | | | | X | | X |
| Telli [229] | 2015 | Observational | | X | X | | | X | | X |
| Tavalaee [230] | 2015 | Observational | | X | | | X | | | |
| Shabana [231] | 2015 | Observational | | X | | | | X | | |
| Abdelaziz [232] | 2015 | Observational | X | X | | | | X | | X |
| Mohammed [233] | 2015 | Observational | | X | | | | X | | X |
| McGarry [234] | 2015 | Observational | | X | | | X | | | |
| Hou [235] | 2015 | Observational | | | X | | | | | |
| Fukuda [236] | 2015 | Observational | X | X | | | X | | X | X |
| Naderi [237] | 2015 | Observational | X | X | | | | | | X |
| Hu [238] | 2015 | Observational | X | X | | X | | | | X |
| Amer [239] | 2015 | Observational | | X | | | X | X | | |
| Lee [240] | 2015 | Observational | | X | | | X | X | | |
| Cantoro [241] | 2015 | Observational | | X | | | X | | | X |
| Pajovic [242] | 2015 | Observational | | | | | X | X | | |
| Ni [243] | 2015 | Observational | | X | | | | X | | X |
| Wang [244] | 2015 | Observational | | X | | | | | | X |
| Binhazzaa [245] | 2016 | Observational | | X | | X | | X | X | X |
| Arab [246] | 2016 | Observational | | X | | | X | | | X |
| Kucuk [247] | 2016 | Observational | | X | | | | X | | X |
| Lv [248] | 2016 | Observational | | X | | | | X | | |
| Ener [249] | 2016 | Observational | | X | | | | | | |
| Karami [250] | 2016 | Observational | | X | | | | | | X |
| Park [251] | 2016 | Observational | | X | | X | | | | X |
| Guo [252] | 2016 | Observational | | X | | | | X | | |
| Barekat [253] | 2016 | Observational | | X | | | X | | | X |
| Sofimajidpour [254] | 2016 | Observational | | X | X | | X | | | X |
| Ariagno [255] | 2016 | Observational | | X | X | | | X | | X |
| Mohamed [256] | 2017 | Observational | X | X | | | | X | | X |
| Samplaski [257] | 2017 | Observational | | | | | | | X | |
| Pijoan [258] | 2017 | Observational | | X | | | X | | | X |
| Mostafa [259] | 2017 | Observational | | X | | | X | X | | |

Table 2. Continued 5

| First author | Year | Study design | Outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Alkandari [260] | 2017 | Observational | | | | | X | | | |
| Morshed [261] | 2017 | Observational | | X | | | X | | | |
| Qu [262] | 2017 | Observational | X | X | | X | | X | | X |
| Akand [263] | 2017 | Observational | | X | | | X | | | |
| Feng [264] | 2017 | Observational | | X | X | | X | | | |
| Gao [265] | 2017 | Observational | | X | X | | X | | | X |
| Gao [266] | 2017 | Observational | | X | X | | X | | | X |
| Afsin [267] | 2018 | Observational | X | X | | | | X | | X |
| Ketabchi [268] | 2018 | Observational | | | X | | | X | | X |
| Vahidi [269] | 2018 | Observational | X | X | | | | | | X |
| Lu [270] | 2018 | Observational | | X | | | | | | X |
| Çayan [271] | 2018 | Observational | | | | | | | X | |
| Gupta [272] | 2018 | Observational | | X | | | X | | | |
| Allameh [273] | 2018 | Observational | | X | | | X | | | X |
| Shafi [274] | 2018 | Observational | | X | | | | X | | X |
| Hosseini [275] | 2018 | Observational | | X | | | | X | | X |
| Sun [276] | 2018 | Observational | X | X | | | | X | | X |
| Dubin [277] | 2018 | Observational | | X | | | X | | X | |
| Liu [278] | 2018 | Observational | X | X | | | | | | X |
| Alenzi [279] | 2019 | Observational | | X | | | X | | | |
| Kızılay [280] | 2019 | Observational | X | X | X | | X | X | X | X |
| Abdulmageed [281] | 2019 | Observational | | X | | | | | | |
| Bolat [282] | 2019 | Observational | | X | | | | | X | X |
| Camargo [283] | 2019 | Observational | X | X | X | | | X | X | X |
| Masterson [284] | 2019 | Observational | | | | | | | X | |
| Ates [285] | 2019 | Observational | X | X | X | | | X | X | |
| Belardin [286] | 2019 | Observational | | X | X | | | X | | X |
| Palmisano [287] | 2019 | Observational | | X | | | | X | | X |
| Abbasi [288] | 2020 | Observational | X | X | | | X | X | | |
| Ilktac [289] | 2020 | Observational | X | | | | | | | X |
| Teng [290] | 2020 | Observational | | X | | | X | | | X |
| Nasser [291] | 2020 | Observational | | X | | | | | | X |
| Abd El Rahman [292] | 2020 | Observational | | X | | | X | | | X |
| Ghaed [293] | 2020 | Observational | X | X | | | | X | | X |
| Habib [294] | 2020 | Observational | | X | | | X | | | |
| Özkaptan [295] | 2020 | Observational | | X | | | X | | | X |
| Kamal [296] | 2020 | Observational | X | X | X | | | X | | |
| Jin [297] | 2020 | Observational | | X | | | X | | | |
| Senturk [298] | 2020 | Observational | | X | | | | | | X |
| Öztekin [299] | 2020 | Observational | X | X | X | | X | X | | |
| Ghanem [300] | 2020 | Observational | | X | | | | X | | X |
| Omar [301] | 2020 | Observational | X | X | | | X | | | X |
| Gok [302] | 2020 | Observational | X | X | | | | X | | X |
| Mostafa [303] | 2020 | Observational | | X | | | X | | | X |
| Alkhamees [304] | 2020 | Observational | | | X | | X | | | X |
| Khan [305] | 2020 | Observational | | | X | | | | | |
| Ok [306] | 2020 | Observational | X | X | X | | X | | X | |

Table 2. Continued 6

| First author | Year | Study design | Outcome | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Phan [307] | 2021 | Observational | | | X | | X | | | |
| Erdogan [308] | 2021 | Observational | | X | | | | X | | |
| Fernández-Concha Schwalb [309] | 2021 | Observational | | X | | | | X | | |
| Kavoussi [310] | 2021 | Observational | X | X | | | X | X | X | |
| Fuschi [311] | 2021 | Observational | | X | | | X | | | X |
| Pazir [312] | 2021 | Observational | | | | | | | X | |
| Shomarufov [313] | 2021 | Observational | X | | | | | | | |
| Morini [314] | 2021 | Observational | X | X | X | | X | X | | X |
| Majzoub [367] | 2021 | Observational | X | X | | | X | X | X | X |
| Hudson [315] | 1985 | Case-control | | X | | | X | | | |
| Hudson [316] | 1986 | Case-control | | X | | | X | | | |
| Giordanengo [317] | 1993 | Case-control | | X | | | X | | | X |
| Yamamoto [318] | 1996 | Case-control | | X | | | X | | X | X |
| Fuse [319] | 1996 | Case-control | | X | | | X | | | |
| Mandressi [320] | 1996 | Case-control | X | | X | | X | | | |
| Koşar [321] | 2000 | Case-control | | X | | | X | | | X |
| Zarrilli [322] | 2000 | Case-control | | X | | | X | X | | |
| Fujisawa [323] | 2003 | Case-control | | X | | | X | | | |
| Salama [324] | 2003 | Case-control | | X | | | | | | |
| Di Bisceglie [325] | 2003 | Case-control | | X | | | | X | | X |
| Gazzera [326] | 2006 | Case-control | | X | | | X | | | X |
| Zini [327] | 2006 | Case-control | | | | | | | X | |
| Di Bisceglie [328] | 2007 | Case-control | | X | | | | X | | X |
| Baazeem [11] | 2009 | Case-control | X | X | | | X | | X | X |
| Ichioka [329] | 2009 | Case-control | | | X | | X | | | |
| Nasr Esfahani [330] | 2010 | Case-control | | X | | | | | | |
| Seo [331] | 2010 | Case-control | X | X | | X | X | | | X |
| Esteves [332] | 2010 | Case-control | X | X | X | | | X | X | X |
| Sathya Srini [333] | 2011 | Case-control | | X | | | | | | |
| Ghanem [334] | 2011 | Case-control | | X | | | | X | | X |
| Sadek [335] | 2011 | Case-control | | X | | | X | | | X |
| Awadallah [336] | 2011 | Case-control | | X | | | X | | | |
| Mohamed [337] | 2011 | Case-control | X | X | | | X | | | |
| Gokce [338] | 2013 | Case-control | | X | X | | X | X | | X |
| Alhathal [339] | 2016 | Case-control | | X | | | | X | | |
| Ni [340] | 2016 | Case-control | | X | | | X | X | | X |
| Chen [341] | 2016 | Case-control | X | X | | | X | | | X |
| Abdelbaki [342] | 2017 | Case-control | X | X | | | X | X | X | X |
| Bou Nasr [343] | 2017 | Case-control | X | X | X | X | X | | X | X |
| Gomaa [344] | 2018 | Case-control | X | X | X | | X | X | | X |
| Turgut [345] | 2020 | Case-control | | X | | | X | | | X |
| El-Ariny [346] | 2020 | Case-control | | X | | | | X | | |
| Fathi [347] | 2021 | Case-control | | X | | | | X | | X |
| El Taieb [348] | 2020 | Case-control | X | X | | | | X | | X |
| Yavetz [349] | 1992 | RCT | | X | X | | X | | | X |
| Sayfan [350] | 1992 | RCT | | | X | | | | | X |
| Breznik [351] | 1993 | RCT | | X | | | X | | | |

Table 2. Continued 7

| First author | Year | Study design | Outcome | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | SV | SC | TC | V | TM | PM | TMSC | SM |
| Nieschlag [352] | 1995 | RCT | | X | | | | | | |
| Unal [353] | 2001 | RCT | | X | | | X | | | X |
| Abdel-Maguid [354] | 2010 | RCT | | X | | | | X | | |
| Abdel-Meguid [355] | 2011 | RCT | | X | | | | X | | X |
| Mansour Ghanaie [356] | 2012 | RCT | | X | X | | | X | | X |
| Azizollahi [357] | 2013 | RCT | | | X | | X | X | | X |
| Akin [358] | 2014 | RCT | | | | | X | | | X |
| Asr Badr [359] | 2017 | RCT | X | | X | | X | | | X |
| Bryniarski [360] | 2017 | RCT | X | X | X | X | X | X | | X |
| Guo [361] | 2017 | RCT | | X | | | X | | | X |
| Abdelsalam [362] | 2017 | RCT | | | | | | X | | |
| Vyas [363] | 2017 | RCT | | X | | | X | | | X |
| Ketabchi [268] | 2018 | RCT | | | X | | | | | |
| Babak [364] | 2018 | RCT | | X | | | X | | | X |
| Zaazaa [365] | 2018 | RCT | | X | X | | X | | | X |
| Almekaty [366] | 2019 | RCT | | X | | | X | | | |

RCT: randomized controlled trial, PM: progressive sperm motility, SC: sperm concentration, SM: sperm morphology, SV: semen volume, TC: total sperm count, TM: total sperm motility, TMSC: total motile sperm count, V: sperm vitality.

Table 3. Quality of evidence assessment[a] for observational and case-control studies

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Haensch [26] | 1976 | Observational | 0 | 3 | 3 | 6 |
| Rodriguez-Rigau [27] | 1978 | Observational | 1 | 3 | 4 | 8 |
| Johnsen [28] | 1978 | Observational | 1 | 3 | 3 | 7 |
| Nilsson [29] | 1979 | Observational | 1 | 3 | 4 | 8 |
| Greenberg [30] | 1979 | Observational | 1 | 3 | 3 | 7 |
| Homonnai [31] | 1980 | Observational | 1 | 3 | 3 | 7 |
| Gogol [32] | 1980 | Observational | 1 | 3 | 3 | 7 |
| Lukkarinen [33] | 1984 | Observational | 2 | 3 | 4 | 9 |
| Foresta [34] | 1984 | Observational | 1 | 2 | 2 | 5 |
| Tinga [35] | 1984 | Observational | 1 | 2 | 1 | 4 |
| Shinoda [36] | 1985 | Observational | 1 | 3 | 3 | 7 |
| Marmar [37] | 1985 | Observational | 1 | 3 | 3 | 7 |
| Segenreich [38] | 1986 | Observational | 1 | 3 | 3 | 7 |
| Vereecken [39] | 1986 | Observational | 2 | 2 | 3 | 7 |
| Hadziselimovic [40] | 1986 | Observational | 3 | 3 | 3 | 9 |
| Burke [41] | 1987 | Observational | 1 | 3 | 3 | 7 |
| Nagai [42] | 1988 | Observational | 1 | 2 | 3 | 6 |
| Okuyama [43] | 1988 | Observational | 1 | 3 | 6 | 10 |
| Gerris [44] | 1988 | Observational | 1 | 3 | 3 | 7 |
| Yarborough [45] | 1989 | Observational | 0 | 2 | 3 | 5 |
| Parsch [46] | 1990 | Observational | 1 | 2 | 4 | 7 |
| Kuroiwa [47] | 1991 | Observational | 1 | 3 | 3 | 7 |
| Dhabuwala [48] | 1992 | Observational | 2 | 2 | 4 | 8 |

Table 3. Continued 1

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Donovanjr [49] | 1992 | Observational | 0 | 3 | 3 | 6 |
| Ito [50] | 1993 | Observational | 1 | 2 | 4 | 7 |
| Steckel [51] | 1993 | Observational | 1 | 3 | 4 | 8 |
| Ross [52] | 1993 | Observational | 4 | 2 | 3 | 9 |
| Hirokawa [53] | 1993 | Observational | 1 | 2 | 4 | 7 |
| Lerchl [54] | 1993 | Observational | 0 | 3 | 4 | 7 |
| Kondoh [55] | 1993 | Observational | 1 | 3 | 4 | 8 |
| Yamamoto [56] | 1994 | Observational | 3 | 3 | 3 | 9 |
| Dewire [57] | 1994 | Observational | 3 | 2 | 4 | 9 |
| Knudson [58] | 1994 | Observational | 0 | 3 | 4 | 7 |
| Nakada [59] | 1994 | Observational | 1 | 2 | 3 | 6 |
| Yamamoto [60] | 1995 | Observational | 1 | 2 | 4 | 7 |
| Ferguson [61] | 1995 | Observational | 1 | 2 | 3 | 6 |
| Chiang [62] | 1995 | Observational | 1 | 2 | 4 | 7 |
| Segenreich [63] | 1995 | Observational | 2 | 3 | 3 | 8 |
| Marmar [37] | 1995 | Observational | 0 | 2 | 4 | 6 |
| Watanabe [64] | 1995 | Observational | 1 | 3 | 3 | 7 |
| Su [65] | 1995 | Observational | 3 | 2 | 1 | 6 |
| Parikh [66] | 1996 | Observational | 1 | 2 | 6 | 9 |
| Jarow [67] | 1996 | Observational | 1 | 3 | 3 | 7 |
| Punekar [68] | 1996 | Observational | 2 | 3 | 4 | 9 |
| Takahara [69] | 1996 | Observational | 1 | 3 | 4 | 8 |
| Atikeler [70] | 1996 | Observational | 1 | 3 | 4 | 8 |
| Vazquez-Levin [71] | 1997 | Observational | 4 | 2 | 3 | 9 |
| Segenreich [72] | 1997 | Observational | 1 | 2 | 3 | 6 |
| Seftel [73] | 1997 | Observational | 2 | 2 | 4 | 8 |
| Hauser [74] | 1997 | Observational | 2 | 3 | 3 | 8 |
| Bablok [75] | 1997 | Observational | 1 | 2 | 3 | 6 |
| Nozawa [76] | 1997 | Observational | 1 | 2 | 4 | 7 |
| Johnsen [77] | 1997 | Observational | 2 | 3 | 3 | 8 |
| Flati [78] | 1997 | Observational | 2 | 3 | 3 | 8 |
| Barbalias [79] | 1998 | Observational | 2 | 3 | 3 | 8 |
| Abdulmaaboud [80] | 1998 | Observational | 1 | 2 | 3 | 6 |
| Aşci [81] | 1998 | Observational | 1 | 2 | 3 | 6 |
| Matthews [82] | 1998 | Observational | 2 | 3 | 6 | 11 |
| Schatte [83] | 1998 | Observational | 2 | 3 | 3 | 8 |
| Madjar [84] | 1998 | Observational | 1 | 2 | 3 | 6 |
| Ismail [85] | 1999 | Observational | 2 | 2 | 3 | 7 |
| Zini [86] | 1999 | Observational | 1 | 3 | 3 | 7 |
| Kim [87] | 1999 | Observational | 1 | 3 | 3 | 7 |
| Scherr [88] | 1999 | Observational | 1 | 3 | 4 | 8 |
| Uygur [89] | 1999 | Observational | 1 | 3 | 3 | 7 |
| Chiang [90] | 1999 | Observational | 0 | 3 | 4 | 7 |
| Reichart [91] | 2000 | Observational | 2 | 3 | 4 | 9 |
| Grasso [92] | 2000 | Observational | 2 | 3 | 4 | 9 |
| Pianalto [93] | 2000 | Observational | 2 | 2 | 3 | 7 |

Table 3. Continued 2

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Cayan [94] | 2000 | Observational | 3 | 3 | 4 | 10 |
| Papanikolaou [95] | 2000 | Observational | 1 | 2 | 3 | 6 |
| Pierik [96] | 1998 | Observational | 3 | 3 | 3 | 9 |
| Kamal [97] | 2001 | Observational | 2 | 2 | 3 | 7 |
| Cayan [98] | 2001 | Observational | 0 | 2 | 3 | 5 |
| Mostafa [99] | 2001 | Observational | 2 | 2 | 3 | 7 |
| Jungwirth [100] | 2001 | Observational | 2 | 3 | 3 | 8 |
| Cavallaro [101] | 2001 | Observational | 3 | 3 | 4 | 10 |
| Avila-Vergara [102] | 2001 | Observational | 1 | 2 | 3 | 6 |
| Cayan [103] | 2002 | Observational | 2 | 2 | 1 | 5 |
| Kibar [104] | 2002 | Observational | 3 | 2 | 3 | 8 |
| Onozawa [105] | 2002 | Observational | 3 | 2 | 4 | 9 |
| Iwasaki [106] | 2003 | Observational | 1 | 3 | 3 | 7 |
| Hsieh [107] | 2003 | Observational | 2 | 3 | 3 | 8 |
| Younes [108] | 2003 | Observational | 1 | 3 | 3 | 7 |
| Fuse [109] | 2003 | Observational | 3 | 2 | 4 | 9 |
| Nuhoğlu [110] | 2004 | Observational | 2 | 3 | 3 | 8 |
| Ishikawa [111] | 2004 | Observational | 1 | 2 | 3 | 6 |
| O'Brien [112] | 2004 | Observational | 1 | 2 | 3 | 6 |
| Polito [113] | 2004 | Observational | 3 | 3 | 3 | 9 |
| Flati [114] | 2004 | Observational | 2 | 3 | 3 | 8 |
| Grober [115] | 2004 | Observational | 2 | 3 | 3 | 8 |
| Grober [116] | 2004 | Observational | 2 | 2 | 3 | 7 |
| Gat [117] | 2004 | Observational | 2 | 3 | 3 | 8 |
| Gat [118] | 2004 | Observational | 2 | 3 | 3 | 8 |
| Gat [119] | 2004 | Observational | 3 | 3 | 3 | 9 |
| Ortapamuk [120] | 2005 | Observational | 1 | 3 | 4 | 8 |
| Ketabchi [121] | 2005 | Observational | 2 | 3 | 3 | 8 |
| Watanabe [122] | 2005 | Observational | 1 | 3 | 3 | 7 |
| Nasr-Esfahani [123] | 2005 | Observational | 2 | 3 | 4 | 9 |
| Yeşilli [124] | 2005 | Observational | 1 | 3 | 4 | 8 |
| Mancini [125] | 2005 | Observational | 1 | 3 | 4 | 8 |
| Pasqualotto [126] | 2005 | Observational | 1 | 3 | 3 | 7 |
| Ishikawa [127] | 2005 | Observational | 2 | 2 | 3 | 7 |
| Zini [128] | 2005 | Observational | 4 | 2 | 3 | 9 |
| Benoff [129] | 2005 | Observational | 3 | 3 | 4 | 10 |
| Pasqualotto [130] | 2005 | Observational | 1 | 3 | 3 | 7 |
| Ku [131] | 2005 | Observational | 1 | 2 | 3 | 6 |
| Pasqualotto [132] | 2005 | Observational | 1 | 3 | 3 | 7 |
| Mehrsai [133] | 2005 | Observational | 1 | 3 | 3 | 7 |
| Orhan [134] | 2005 | Observational | 1 | 3 | 3 | 7 |
| Libman [135] | 2006 | Observational | 1 | 2 | 3 | 6 |
| Ramasamy [136] | 2006 | Observational | 2 | 3 | 4 | 9 |
| Hussein [137] | 2006 | Observational | 2 | 3 | 4 | 9 |
| Zucchi [138] | 2006 | Observational | 2 | 2 | 4 | 8 |
| Hsieh [139] | 2006 | Observational | 1 | 3 | 3 | 7 |

Table 3. Continued 3

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Baccetti [140] | 2006 | Observational | 1 | 3 | 4 | 8 |
| Djaladat [141] | 2006 | Observational | 1 | 3 | 3 | 7 |
| Shin [142] | 2006 | Observational | 0 | 2 | 3 | 5 |
| Ashrafi [143] | 2007 | Observational | 2 | 3 | 4 | 9 |
| Okeke [144] | 2007 | Observational | 1 | 2 | 3 | 6 |
| Qadan [145] | 2007 | Observational | 2 | 3 | 3 | 8 |
| Zini [146] | 2008 | Observational | 4 | 3 | 4 | 11 |
| Ozden [147] | 2008 | Observational | 3 | 2 | 4 | 9 |
| Flacke [148] | 2008 | Observational | 1 | 3 | 4 | 8 |
| Al-Said [149] | 2008 | Observational | 4 | 3 | 6 | 13 |
| Atalay [150] | 2008 | Observational | 1 | 3 | 4 | 8 |
| Cakan [151] | 2008 | Observational | 3 | 2 | 6 | 11 |
| Balci [152] | 2008 | Observational | 1 | 2 | 3 | 6 |
| Gandini [153] | 2008 | Observational | 2 | 2 | 3 | 7 |
| Chen [154] | 2008 | Observational | 2 | 3 | 3 | 8 |
| Agnifili [155] | 2008 | Observational | 2 | 3 | 3 | 8 |
| Juárez-Albarrán [156] | 2008 | Observational | 1 | 3 | 3 | 7 |
| Kadhim [157] | 2009 | Observational | 2 | 3 | 4 | 9 |
| Elbendary [158] | 2009 | Observational | 3 | 3 | 4 | 10 |
| Shamsa [159] | 2009 | Observational | 2 | 2 | 4 | 8 |
| Hafez [160] | 2009 | Observational | 2 | 2 | 4 | 8 |
| Salem [161] | 2009 | Observational | 2 | 2 | 4 | 8 |
| Jasemi [162] | 2009 | Observational | 3 | 2 | 3 | 8 |
| Zheng [163] | 2009 | Observational | 3 | 3 | 4 | 10 |
| Nasr-Esfahani [164] | 2009 | Observational | 3 | 3 | 3 | 9 |
| Zorba [165] | 2009 | Observational | 3 | 2 | 3 | 8 |
| Kondo [166] | 2009 | Observational | 2 | 3 | 3 | 8 |
| Acar [167] | 2009 | Observational | 2 | 3 | 3 | 8 |
| Fall [168] | 2010 | Observational | 2 | 3 | 3 | 8 |
| Al-Adl [169] | 2010 | Observational | 1 | 2 | 3 | 6 |
| Abdelwahab [170] | 2010 | Observational | 3 | 3 | 4 | 10 |
| Li [171] | 2010 | Observational | 1 | 3 | 3 | 7 |
| Dadfar [172] | 2010 | Observational | 3 | 3 | 3 | 9 |
| Al-Ghazo [173] | 2011 | Observational | 1 | 2 | 3 | 6 |
| Azadi [174] | 2011 | Observational | 1 | 3 | 6 | 10 |
| Abd Ellatif [175] | 2011 | Observational | 3 | 3 | 6 | 12 |
| Giagulli [176] | 2011 | Observational | 3 | 3 | 6 | 12 |
| Cho [177] | 2011 | Observational | 2 | 2 | 3 | 7 |
| Chen [178] | 2011 | Observational | 3 | 3 | 3 | 9 |
| Zini [179] | 2011 | Observational | 3 | 3 | 3 | 9 |
| Hsiao [180] | 2011 | Observational | 4 | 2 | 3 | 9 |
| Ghazi [181] | 2011 | Observational | 2 | 3 | 3 | 8 |
| Tarhan [182] | 2011 | Observational | 3 | 3 | 3 | 9 |
| Ozturk [183] | 2012 | Observational | 3 | 2 | 2 | 7 |
| Mohamid [184] | 2012 | Observational | 2 | 3 | 3 | 8 |
| Shiraishi [185] | 2012 | Observational | 2 | 2 | 3 | 7 |

Table 3. Continued 4

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Li [186] | 2012 | Observational | 2 | 2 | 3 | 7 |
| Tavalaee [187] | 2012 | Observational | 2 | 2 | 3 | 7 |
| Pirinççi [188] | 2012 | Observational | 2 | 2 | 3 | 7 |
| Gabriel [189] | 2012 | Observational | 3 | 3 | 3 | 9 |
| Mehraban [190] | 2012 | Observational | 2 | 3 | 3 | 8 |
| El-Haggar [191] | 2012 | Observational | 2 | 3 | 3 | 8 |
| La Vignera [192] | 2012 | Observational | 3 | 3 | 3 | 9 |
| Ozturk [183] | 2012 | Observational | 3 | 3 | 3 | 9 |
| Navaeian-Kalat [193] | 2012 | Observational | 2 | 3 | 3 | 8 |
| Armağan [194] | 2012 | Observational | 2 | 2 | 3 | 7 |
| Kim [195] | 2012 | Observational | 0 | 3 | 3 | 6 |
| Keyhan [196] | 2012 | Observational | 2 | 3 | 3 | 8 |
| Abdelrahman [197] | 2012 | Observational | 1 | 3 | 3 | 7 |
| Al Bakri [198] | 2012 | Observational | 1 | 2 | 3 | 6 |
| Lee [199] | 2011 | Observational | 2 | 3 | 3 | 8 |
| Sun [200] | 2012 | Observational | 2 | 3 | 3 | 8 |
| Ollandini [201] | 2013 | Observational | 2 | 3 | 3 | 8 |
| Leung [202] | 2013 | Observational | 1 | 2 | 3 | 6 |
| Bonyadi [203] | 2013 | Observational | 1 | 3 | 3 | 7 |
| Smit [204] | 2013 | Observational | 3 | 3 | 3 | 9 |
| Camargo [205] | 2013 | Observational | 2 | 3 | 3 | 8 |
| Zhang [206] | 2014 | Observational | 2 | 3 | 3 | 8 |
| Kang [207] | 2013 | Observational | 3 | 3 | 3 | 9 |
| Bozhedomov [208] | 2014 | Observational | 3 | 3 | 3 | 9 |
| Camargo [209] | 2014 | Observational | 2 | 3 | 3 | 8 |
| Prasivoravong [210] | 2014 | Observational | 3 | 3 | 3 | 9 |
| Komiya [211] | 2014 | Observational | 3 | 2 | 3 | 8 |
| Wang [212] | 2014 | Observational | 4 | 3 | 3 | 10 |
| Enatsu [213] | 2014 | Observational | 2 | 2 | 3 | 7 |
| Samplaski [214] | 2014 | Observational | 2 | 2 | 3 | 7 |
| Hosseinifar [215] | 2014 | Observational | 2 | 3 | 3 | 8 |
| Kadioglu [216] | 2014 | Observational | 3 | 2 | 3 | 8 |
| Lehtihet [217] | 2014 | Observational | 2 | 3 | 3 | 8 |
| Al-Adl [218] | 2014 | Observational | 3 | 3 | 3 | 9 |
| Li [219] | 2014 | Observational | 1 | 3 | 3 | 7 |
| Chen [220] | 2014 | Observational | 2 | 2 | 3 | 7 |
| Lee [221] | 2014 | Observational | 1 | 3 | 3 | 7 |
| Choe [222] | 2015 | Observational | 3 | 2 | 3 | 8 |
| Guo [223] | 2015 | Observational | 3 | 3 | 3 | 9 |
| Kiziler [224] | 2015 | Observational | 3 | 3 | 3 | 9 |
| Zhang [225] | 2015 | Observational | 3 | 3 | 3 | 9 |
| Youssef [226] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Cantoro [227] | 2015 | Observational | 3 | 3 | 3 | 9 |
| Ener [228] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Telli [229] | 2015 | Observational | 3 | 3 | 3 | 9 |
| Tavalaee [230] | 2015 | Observational | 2 | 3 | 3 | 8 |

Table 3. Continued 5

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Shabana [231] | 2015 | Observational | 3 | 3 | 3 | 9 |
| Abdelaziz [232] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Mohammed [233] | 2015 | Observational | 3 | 3 | 3 | 9 |
| McGarry [234] | 2015 | Observational | 3 | 2 | 4 | 9 |
| Hou [235] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Fukuda [236] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Naderi [237] | 2015 | Observational | 2 | 2 | 3 | 7 |
| Hu [238] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Amer [239] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Lee [240] | 2015 | Observational | 2 | 2 | 3 | 7 |
| Cantoro [241] | 2015 | Observational | 3 | 3 | 6 | 12 |
| Pajovic [242] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Ni [243] | 2015 | Observational | 3 | 3 | 4 | 10 |
| Wang [244] | 2015 | Observational | 2 | 3 | 3 | 8 |
| Binhazzaa [245] | 2016 | Observational | 3 | 3 | 3 | 9 |
| Arab [246] | 2016 | Observational | 2 | 2 | 3 | 7 |
| Kucuk [247] | 2016 | Observational | 3 | 3 | 3 | 9 |
| Lv [248] | 2016 | Observational | 2 | 3 | 3 | 8 |
| Ener [249] | 2016 | Observational | 2 | 3 | 3 | 8 |
| Karami [250] | 2016 | Observational | 2 | 3 | 3 | 8 |
| Park [251] | 2016 | Observational | 2 | 3 | 3 | 8 |
| Guo [252] | 2016 | Observational | 3 | 3 | 3 | 9 |
| Barekat [253] | 2016 | Observational | 3 | 3 | 3 | 9 |
| Sofimajidpour [254] | 2016 | Observational | 2 | 3 | 3 | 8 |
| Ariagno [255] | 2016 | Observational | 3 | 3 | 3 | 9 |
| Mohamed [256] | 2017 | Observational | 1 | 3 | 3 | 7 |
| Samplaski [257] | 2017 | Observational | 2 | 2 | 3 | 7 |
| Pijoan [258] | 2017 | Observational | 1 | 3 | 4 | 8 |
| Mostafa [259] | 2017 | Observational | 1 | 3 | 3 | 7 |
| Alkandari [260] | 2017 | Observational | 1 | 3 | 3 | 7 |
| Morshed [261] | 2017 | Observational | 2 | 2 | 3 | 7 |
| Qu [262] | 2017 | Observational | 3 | 3 | 3 | 9 |
| Akand [263] | 2017 | Observational | 3 | 3 | 3 | 9 |
| Feng [264] | 2017 | Observational | 4 | 2 | 6 | 12 |
| Gao [265] | 2017 | Observational | 4 | 2 | 6 | 12 |
| Gao [266] | 2017 | Observational | 1 | 2 | 4 | 7 |
| Afsin [267] | 2018 | Observational | 3 | 3 | 3 | 9 |
| Ketabchi [268] | 2018 | Observational | 3 | 3 | 3 | 9 |
| Vahidi [269] | 2018 | Observational | 2 | 3 | 3 | 8 |
| Lu [270] | 2018 | Observational | 2 | 3 | 3 | 8 |
| Çayan [271] | 2018 | Observational | 2 | 3 | 3 | 8 |
| Gupta [272] | 2018 | Observational | 2 | 2 | 3 | 7 |
| Allameh [273] | 2018 | Observational | 3 | 3 | 3 | 9 |
| Shafi [274] | 2018 | Observational | 1 | 2 | 3 | 6 |
| Hosseini [275] | 2018 | Observational | 1 | 2 | 3 | 6 |
| Sun [276] | 2018 | Observational | 2 | 3 | 3 | 8 |

Table 3. Continued 6

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Dubin [277] | 2018 | Observational | 1 | 2 | 3 | 6 |
| Liu [278] | 2018 | Observational | 1 | 2 | 3 | 6 |
| Alenzi [279] | 2019 | Observational | 3 | 2 | 3 | 8 |
| Kızılay [280] | 2019 | Observational | 2 | 3 | 3 | 8 |
| Abdulmageed [281] | 2019 | Observational | 2 | 3 | 3 | 8 |
| Bolat [282] | 2019 | Observational | 2 | 2 | 3 | 7 |
| Camargo [283] | 2019 | Observational | 1 | 3 | 3 | 7 |
| Masterson [284] | 2019 | Observational | 1 | 3 | 3 | 7 |
| Ates [285] | 2019 | Observational | 1 | 2 | 3 | 6 |
| Belardin [286] | 2019 | Observational | 1 | 3 | 3 | 7 |
| Palmisano [287] | 2019 | Observational | 1 | 3 | 3 | 7 |
| Abbasi [288] | 2020 | Observational | 1 | 2 | 3 | 6 |
| Ilktac [289] | 2020 | Observational | 1 | 2 | 3 | 6 |
| Teng [290] | 2020 | Observational | 2 | 2 | 3 | 7 |
| Nasser [291] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Abd El Rahman [292] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Ghaed [293] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Habib [294] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Özkaptan [295] | 2020 | Observational | 1 | 2 | 3 | 6 |
| Kamal [296] | 2020 | Observational | 2 | 3 | 6 | 11 |
| Jin [297] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Senturk [298] | 2020 | Observational | 1 | 2 | 3 | 6 |
| Öztekin [299] | 2020 | Observational | 1 | 2 | 3 | 6 |
| Ghanem [300] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Omar [301] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Gok [302] | 2020 | Observational | 2 | 3 | 3 | 8 |
| Mostafa [303] | 2020 | Observational | 2 | 3 | 3 | 8 |
| Alkhamees [304] | 2020 | Observational | 3 | 2 | 3 | 8 |
| Khan [305] | 2020 | Observational | 1 | 3 | 3 | 7 |
| Ok [306] | 2020 | Observational | 3 | 2 | 3 | 8 |
| Phan [307] | 2021 | Observational | 0 | 3 | 3 | 6 |
| Erdogan [308] | 2021 | Observational | 2 | 2 | 3 | 7 |
| Fernández-Concha Schwalb [309] | 2021 | Observational | 1 | 2 | 4 | 7 |
| Kavoussi [310] | 2021 | Observational | 1 | 2 | 4 | 7 |
| Fuschi [311] | 2021 | Observational | 3 | 3 | 3 | 9 |
| Pazir [312] | 2021 | Observational | 1 | 2 | 3 | 6 |
| Shomarufov [313] | 2021 | Observational | 1 | 2 | 3 | 6 |
| Morini [314] | 2021 | Observational | 2 | 2 | 3 | 7 |
| Majzoub [367] | 2021 | Observational | 2 | 2 | 3 | 7 |
| Hudson [315] | 1985 | Case-control | 0 | 3 | 4 | 7 |
| Hudson [316] | 1986 | Case-control | 0 | 3 | 4 | 7 |
| Giordanengo [317] | 1993 | Case-control | 2 | 2 | 6 | 10 |
| Yamamoto [318] | 1996 | Case-control | 2 | 3 | 6 | 11 |
| Fuse [319] | 1996 | Case-control | 1 | 3 | 4 | 8 |
| Mandressi [320] | 1996 | Case-control | 2 | 3 | 6 | 11 |
| Koşar [321] | 2000 | Case-control | 2 | 3 | 4 | 9 |

Table 3. Continued 6

| First Author | Year | Type of study | Cambridge Quality Checklist | | | Total quality score (2–15) |
|---|---|---|---|---|---|---|
| | | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | |
| Zarrilli [322] | 2000 | Case-control | 2 | 3 | 4 | 9 |
| Fujisawa [323] | 2003 | Case-control | 3 | 3 | 4 | 10 |
| Salama [324] | 2003 | Case-control | 1 | 3 | 4 | 8 |
| Di Bisceglie [325] | 2003 | Case-control | 3 | 2 | 4 | 9 |
| Gazzera [326] | 2006 | Case-control | 3 | 3 | 4 | 10 |
| Zini [327] | 2006 | Case-control | 3 | 2 | 4 | 9 |
| Di Bisceglie [328] | 2007 | Case-control | 1 | 3 | 6 | 10 |
| Baazeem [11] | 2009 | Case-control | 2 | 3 | 4 | 9 |
| Ichioka [329] | 2009 | Case-control | 2 | 1 | 4 | 7 |
| Nasr Esfahani [330] | 2010 | Case-control | 2 | 3 | 6 | 11 |
| Seo [331] | 2010 | Case-control | 0 | 2 | 6 | 8 |
| Esteves [332] | 2010 | Case-control | 2 | 2 | 6 | 10 |
| Sathya Srini [333] | 2011 | Case-control | 1 | 3 | 6 | 10 |
| Ghanem [334] | 2011 | Case-control | 2 | 3 | 6 | 11 |
| Sadek [335] | 2011 | Case-control | 3 | 3 | 4 | 10 |
| Awadallah [336] | 2011 | Case-control | 3 | 3 | 4 | 10 |
| Mohamed [337] | 2011 | Case-control | 1 | 3 | 6 | 10 |
| Gokce [338] | 2013 | Case-control | 1 | 2 | 6 | 9 |
| Alhathal [339] | 2016 | Case-control | 2 | 3 | 3 | 8 |
| Ni [340] | 2016 | Case-control | 3 | 3 | 4 | 10 |
| Chen [341] | 2016 | Case-control | 3 | 3 | 3 | 9 |
| Abdelbaki [342] | 2017 | Case-control | 2 | 3 | 4 | 9 |
| Bou Nasr [343] | 2017 | Case-control | 1 | 3 | 3 | 7 |
| Gomaa [344] | 2018 | Case-control | 2 | 3 | 6 | 11 |
| Turgut [345] | 2020 | Case-control | 1 | 2 | 4 | 7 |
| El-Ariny [346] | 2020 | Case-control | 2 | 3 | 4 | 9 |
| Fathi [347] | 2021 | Case-control | 2 | 3 | 4 | 9 |
| El Taieb [348] | 2020 | Case-control | 1 | 3 | 4 | 8 |

[a]Results of the Cambridge Quality Checklist (Murray et al [18], 2009).

before parameters (SMD 0.203, 95% CI: 0.129–0.278; p<0.001), in the presence of significant inter-study heterogeneity ($I^2$=83.62%). Furthermore, Egger's test demonstrated no significant publication bias (p=0.3329) (Table 5).

## 2. Sperm concentration

The before-after analysis of sperm concentration included 303 articles, for a total of 32,577 infertile patients before and 31,771 after varicocele repair. It showed a significant improvement of the sperm concentration following varicocele repair (SMD 1.590, 95% CI: 1.474–1.706; p<0.001), in the presence of significant inter-study heterogeneity ($I^2$=97.86). Furthermore, evidence of publication bias was found with the Egger's test (p<0.0001) (Table 5).

## 3. Total sperm count

The analysis of the total sperm count was performed on 63 articles, for a total of 5,593 patients with clinical varicocele before and 5,337 after varicocele repair. We found a significant increase in the total sperm count following varicocele repair (SMD 1.824, 95% CI: 1.526–2.121; p<0.001). The test for heterogeneity revealed the presence of significant inter-study heterogeneity ($I^2$=97.88%). A significant publication bias was found in the results of Egger's test (p=0.0063) (Table 5).

## 4. Total motile sperm count

Overall, the analysis of this outcome was performed

Table 4. Quality of evidence assessment[a] for randomized controlled trials

| First author | Year | Cambridge Quality Checklist | | | | CONSORT guidelines (1–25) | Jadad score (1–5) | Total quality score (2–53) |
|---|---|---|---|---|---|---|---|---|
| | | Checklist for correlates | Checklist for risk factors | Checklist for causal risk factor | Cochrane risk of bias for RCTs (7–21) | | | |
| Yavetz [349] | 1992 | 3 | 3 | 7 | 2 | 17 | 2 | 34 |
| Sayfan [350] | 1992 | 2 | 3 | 7 | 2 | 18 | 2 | 34 |
| Breznik [351] | 1993 | 1 | 3 | 7 | 1 | 14 | 2 | 28 |
| Yamamoto [60] | 1995 | 2 | 3 | 7 | 1 | 16 | 1 | 30 |
| Nieschlag [352] | 1995 | 2 | 3 | 7 | 1 | 14 | 3 | 30 |
| Grasso [92] | 1997 | 2 | 3 | 7 | 1 | 16 | 2 | 31 |
| Unal [353] | 2001 | 3 | 3 | 4 | 1 | 8 | 1 | 20 |
| Alkandari [260] | 2017 | 3 | 3 | 7 | 3 | 14 | 1 | 31 |
| Al-Said [149] | 2008 | 3 | 3 | 7 | 3 | 14 | 2 | 32 |
| Abdel-Maguid [354] | 2010 | 2 | 3 | 7 | 1 | 6 | 1 | 20 |
| Abdel-Meguid [355] | 2011 | 3 | 3 | 7 | 1 | 23 | 5 | 42 |
| Mansour Ghanaie [356] | 2012 | 4 | 3 | 7 | 1 | 14 | 1 | 30 |
| Azizollahi [357] | 2013 | 1 | 3 | 7 | 1 | 14 | 2 | 28 |
| Akin [358] | 2014 | 2 | 3 | 7 | 1 | 12 | 1 | 26 |
| Asr Badr [359] | 2017 | 2 | 3 | 7 | 1 | 16 | 3 | 32 |
| Bryniarski [360] | 2017 | 2 | 3 | 7 | 1 | 18 | 1 | 32 |
| Guo [361] | 2017 | 2 | 3 | 7 | 2 | 19 | 3 | 36 |
| Abdelsalam [362] | 2017 | 3 | 3 | 7 | 1 | 11 | 1 | 26 |
| Vyas [363] | 2017 | 2 | 3 | 7 | 1 | 16 | 3 | 32 |
| Ketabchi [268] | 2018 | 3 | 3 | 7 | 1 | 15 | 1 | 30 |
| Babak [364] | 2018 | 2 | 3 | 7 | 1 | 16 | 3 | 32 |
| Zaazaa [365] | 2018 | 2 | 3 | 7 | 1 | 15 | 1 | 29 |
| Almekaty [366] | 2019 | 2 | 3 | 7 | 1 | 17 | 3 | 33 |

RCT: randomized controlled trial.
[a]Results of the Cambridge Quality Checklist (Murray et al [18], 2009), Cochrane risk of bias for randomized controlled trials (Sterne et al [19], 2016), CONSORT guidelines (Schulz et al [21], 2010), and Jadad score (Jadad et al [20], 1996).

on 50 articles, a total of 6,396 infertile patients with clinical varicocele before and 6,274 after varicocele repair were included in the analysis of total sperm count. We found a significant improvement in the total sperm count following varicocele repair (SMD 1.643, 95% CI: 1.318–1.968; p<0.001), and the presence of significant inter-study heterogeneity ($I^2$=98.65%). The presence of publication bias was shown by Egger's test (p=0.0003) (Table 5).

## 5. Progressive sperm motility

The effect of varicocele repair on progressive sperm motility in infertile patients with clinical varicocele was evaluated in 99 articles, using a before-after approach. The analysis was performed on 10,454 participants before and 10,252 participants after varicocele repair. The results of the meta-analysis showed that varicocele repair was associated with increased sperm progressive motility (SMD 1.845, 95% CI: 1.537–2.153, p<0.001). Heterogeneity across studies was present ($I^2$=98.97%). When one study was excluded, the SMD (95% CI) for sperm progressive motility was 8.125 (4.712–11.538). A significant publication bias was found in the results of Egger's test (p<0.0001) (Table 5).

## 6. Total sperm motility

A total of 209 articles were included for the analysis of this outcome, including 22,326 infertile patients before and 21,898 patients after varicocele repair in the before-after analysis of total motility. Overall, a significant improvement of total sperm motility was detected after varicocele repair (SMD 1.613, 95% CI: 1.467–1.759; p<0.001), in the presence of significant inter-study heterogeneity ($I^2$=97.98%, p<0.001). Evidence of publication bias was found by Egger's test (p<0.001) (Table 5).

Table 5. Results of the before-after varicocele repair analysis of conventional semen parameters

| Parameter | Random | Before (n) | After (n) | SMD | 95% CI | p | Heterogeneity | | Publication bias |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | $I^2$ | p | Egger's test |
| Semen volume | Random | 12,566 | 10,825 | 0.203 | 0.129 to 0.278 | <0.001 | 83.62% | <0.001 | 0.3329 |
| Sperm concentration | Random | 32,577 | 31,771 | 1.590 | 1.474 to1.706 | <0.001 | 97.86% | <0.0001 | <0.0001 |
| Total sperm count | Random | 5,593 | 5,337 | 1.824 | 1.526 to 2.121 | <0.0001 | 97.88% | <0.0001 | 0.0063 |
| TMSC | Random | 6,396 | 6,274 | 1.643 | 1.318 to 1.968 | <0.001 | 98.65% | <0.0001 | 0.0003 |
| Progressive sperm motility | Random | 10,454 | 10,252 | 1.845 | 1.537 to 2.153 | <0.001 | 98.97% | <0.0001 | <0.0001 |
| Total sperm motility | Random | 22,326 | 21,898 | 1.613 | 1.467 to 1.759 | <0.001 | 97.98% | <0.0001 | <0.0001 |
| Sperm morphology | Random | 21,979 | 21,335 | 1.066 | 0.922 to 1.211 | <0.001 | 97.87% | <0.001 | 0.1864 |
| Sperm vitality | Random | 597 | 555 | -1.310 | -2.112 to -0.509 | 0.001 | 98.50% | <0.0001 | 0.0807 |

SMD: standard mean difference, TMSC: total motile sperm count.

### 7. Sperm morphology

A total of 195 articles were included in the analysis of sperm morphology, including 21,979 patients before and 21,335 after varicocele repair was included in the before-after analysis. The effects of varicocele repair on sperm morphology are summarized in Table 5. Overall, a significant improvement of sperm morphology was noted after varicocele repair (SMD 1.066, 95% CI: 0.992–1.211; p<0.001), in the presence of significant inter-study heterogeneity ($I^2$=97.87%). No evidence of publication bias was found.

### 8. Sperm vitality

Fourteen studies reported sperm vitality and were included in our analysis. A total of 1,152 infertile patients with clinical varicocele were included: 597 patients before varicocele repair and 555 patients after varicocele repair. The analysis showed a significant negative effect of varicocele repair on sperm vitality (SMD -1.310, 95% CI: -2.112 to -0.509; p=0.001). There was considerable heterogeneity between studies ($I^2$=98.50%, p<0.0001), and no publication bias was evident as the Egger's test was non-significant (p=0.0807) (Table 5).

## DISCUSSION

Varicocele is a very common condition, affecting one in six males of the general population [1]. In infertile patients, its prevalence is even higher, being diagnosed in 19% to 41% of primary infertility and 80% of secondary infertility cases [1]. Therefore, varicocele is considered as a cause of male infertility [7]. Knowing the impact of varicocele repair on human sperm conventional parameters is important for decision-making in the management of varicocele patients.

In the last 30 years, nearly 2,000 original articles have been published on varicocele and about half have evaluated the impact of varicocele and varicocele repair on semen parameters [368]. Accordingly, varicocele remains one of the most controversial topics in male infertility. Although most international urology and reproductive societies agree on the indication for varicocele repair in cases of male infertility as with clinically palpable varicocele and abnormal semen parameters [8], there are still some clinicians who doubt the beneficial effect of varicocele repair on semen parameters and fertility status [369-371]. According to the results of the current meta-analysis, almost all semen parameters, including semen volume, sperm concentration, total sperm count, total motile sperm count, progressive sperm motility, total sperm motility, and sperm morphology, increase significantly in infertile patients with clinical varicocele following varicocele repair compared to the before-intervention values. Only sperm vitality showed a significant decrease following varicocele repair; the reason for this finding is not clear.

An earlier meta-analysis evaluated the efficacy of varicocele repair in improving the semen parameters of patients with unilateral or bilateral varicocele and at least one abnormal sperm parameter. A significant increase in sperm concentration by $9.71\times10^6$/mL (95% CI: 7.34–12.08, p<0.00001), and sperm progressive motility by 9.92 (95% CI: 4.90–14.95, p=0.0001), was demonstrated following inguinal microsurgical varicocele repair [372]. In the same study, high ligation varicocelectomy was also associated with statistically significant improvements in sperm concentration by $2.03\times10^6$/mL (95% CI: 5.71–18.35, p=0.0002), and motility by 11.72% (95% CI: 4.33–19.12, p=0.002). A statistically

significant improvement in sperm morphology was also associated with both surgical methods (3.16%, 95% CI: 0.72–5.60, p<0.01). Another meta-analysis showed that varicocele repair significantly improves sperm motility and concentration in infertile male with preoperative abnormal sperm parameters and palpable varicocele [373]. In another meta-analysis published in 2011, varicocelectomy was associated with a significant increase in sperm concentration (random-effect model combined improvement 12.32×$10^6$ sperm/mL; 95% CI 9.45–15.19, p<0.0001), progressive (improvement 9.69%; 95% CI 4.86–14.52, p=0.003) and total sperm motility (improvement 10.86%; 95% CI 7.07–14.65, p<0.0001) [11]. However, in that meta-analysis, the included studies displayed significant heterogeneity in terms of patients' characteristics, treatment modality (including radiologic embolization), and diagnostic criteria. In a subsequent meta-analysis, Schauer et al [374] compared the impact of three different surgical techniques for varicocele repair on semen parameters. Regardless of the surgical technique, a statistically significant improvement was observed in sperm concentration (by 7.17 to 10.85×$10^6$/mL) and motility (by 6.80% to 12.25%). The positive impact of varicocelectomy on sperm concentration and sperm motility is also supported by the findings from Birowo et al [375] and Majzoub et al [367].

In the present meta-analysis, the results of comparing preoperative and postoperative basic semen parameters in thousands of infertile male with clinical varicocele are in favor of varicocele repair as a treatment option to improve conventional semen parameters. These results are in line with the current guidelines of international professional societies. The recent guidelines of AUA/ASRM recommend "varicocele repair of clinical varicoceles in non-azoospermic infertile male with abnormal sperm parameters (moderate recommendation; moderate evidence level)" [8]. Similarly, the guidelines of the EAU recommend varicocele repair in "infertile men with a clinical varicocele, abnormal semen parameters, and otherwise unexplained infertility in a couple where the female partner has a good ovarian reserve to improve fertility rates without other male causes of infertility (strong recommendation; high evidence level)" [7]. The European Academy of Andrology (EAA) advises discussing varicocele treatment in infertile couples whose male partner has a palpable varicocele associated with oligoasthenoteratozoospermia [376].

However, the significant positive impact of varicocele repair on basic sperm parameters observed in the current meta-analysis is limited by the remarkable heterogeneity of the included studies and the notable high risk of publication bias towards studies with a positive outcome. It has been suggested that manuscripts with statistically significant results have a much higher chance of being published than those with null results [377]. Investigators may refrain from submitting negative results leading to non-response bias.

The current meta-analysis is the largest to date and includes 351 studies. In addition, the effect size used in the current meta-analysis is the SMD which is generally preferred over the raw mean difference because it accounts for the heterogeneity in methods of mean calculation by measuring the difference in standardized deviation unit [378]. In addition, it supports the previously published meta-analyses (Table 6) [11,367,372,379,380] which showed significant improvement in all studied semen parameters. Furthermore, the improvement in the semen volume after varicocele repair found in the present meta-analysis of 10,825 cases has not been reported by any study. In line with the above-mentioned evidence, the present study found a significant increase in sperm concentration, total sperm count, total sperm motility and specifically progressive sperm motility, and sperm morphology. Finally, surprisingly, in this meta-analysis sperm vitality was found to be decreased after varicocelectomy, which is contrary to the improved motility that was observed. There is no information about this sperm quality marker in other studies. However, inter-study heterogeneity was found.

The strengths of the current meta-analysis (Fig. 2) include that it is the largest meta-analysis of its kind to date. It is also the first to report on volume and total sperm count. Control data exist in the form of semen parameters of the male in these studies prior to varicocele repair, which helps minimize the number of studies excluded to improve the power of this meta-analysis.

The current meta-analysis assessed changes in conventional semen parameters as the outcome measure; however, the extent of improvement in conventional semen parameters that would be considered significant is not agreed upon. There is marked heterogeneity in the included studies. In addition, this meta-analysis compared intra-person before-after sperm parameters using the patient's parameters before intervention as

Table 6. Evidence coming from previous meta-analyses on varicocele repair

| Reference | Design | No. of studies/sample size | Result | Comment |
|---|---|---|---|---|
| Majzoub et al (2021) [367] | Before-After mean difference (MD) | 8/600 | Sperm count: 5.642 mil/mL (95% CI: 4.195–7.090, p<0.001)<br>Total sperm motility: 7.772% (95% CI: 3.248–12.297, p=0.001)<br>Total motile sperm count: 8.432 mil (95% CI: 4.648–12.228, p<0.001) | Severe oligospermia<br>All observational |
| Birowo et al (2020) [379] | Before-After mean difference (MD) | 7/289 | Sperm concentration: 9.59 mil/mL; 95% CI: 7.80, 11.38; p < 0.00001)<br>Progressive sperm motility: 8.66%; 95% CI: 6.96, 10.36; p < 0.00001)<br>Sperm morphology: 2.73%; 95% CI: 0.65, 4.80; p = 0.01) | |
| Wang et al (2019) [380] | Before-After (MD) | Profound (5/151 patients), severe (2/115 patients), moderate (2/79 patients), and mild (2/248 patients) | <2 million - profound: 10.20 (95% CI: 9.11–11.30, p<0.0001)<br>2–5 million - severe: 15.77 (95% CI: 10.65–20.89, p<0.0001)<br>5–10 million - moderate: 19.18 (95% CI: 10.40–27.96, p<0.0001)<br>>10 million - mild: 49.68 (95% CI: 38.74–60.62, p<0.0001) | Examined total motile sperm count<br>The most significant improvement is in the mild group |
| Baazeem et al (2011) [11] | Before-After (MD) | Sperm concentration: 22<br>Total sperm motility: 17<br>Progressive sperm motility: 5 | Sperm concentration: 12.32 mil/mL (95% CI: 9.45–15.19; p<0.0001)<br>Total sperm motility: 10.86% (95% CI: 7.07–14.65; p<0.0001)<br>Progressive sperm motility: 9.69% (95% CI: 4.86–14.52; p=0.003) | |
| Agarwal et al (2007) [372] | Before-After (MD) | 17 | Microsurgical varicocelectomy:<br>Sperm concentration: 9.71 mil/mL (95% CI: 7.34–12.08, p <0.00001)<br>Sperm progressive motility: 9.92% (95% CI: 4.90–14.95, p=0.0001)<br>High ligation varicocelectomy:<br>Sperm concentration: 12.03 mil/mL (95% CI: 5.71–18.35, p=0.0002)<br>Sperm motility: 11.72% (95% CI: 4.33–19.12, p=0.002)<br>Both:<br>Sperm morphology: 3.16% (95% CI: 0.72–5.60, p=0.01) | |
| Current study | Before-After SMD | 351 | Semen volume: SMD=0.23; p<0.001<br>Sperm concentration: SMD=1.5; p<0.001<br>Total sperm count: SMD=1.8; p<0.001<br>Total motile sperm count: SMD=1.6; p<0.001<br>Total motility: SMD=1.6; p<0.001<br>Progressive motility: SMD=1.8, p<0.001<br>Sperm morphology: SMD=1; p<0.001<br>Sperm vitality: SMD= -1.3; p=0.001 | |

SMD: standardized mean difference.


Fig. 2. Strengths, Weaknesses, Opportunities and Threats (SWOT) Analysis.

the control group. This approach has some drawbacks in terms of statistical methodology [381], potential of the placebo effect, non-blindness of the type of intervention *e.g.,* varicocelectomy, and it also lacks a control arm of patients that did not undergo varicocele repair. A proper control group is a key in establishing a cause-and-effect relationship of a certain variable [382] and testing the impact of an intervention on the outcome. However, this before-after analysis has the advantage of including all intervention groups, thus minimizing the number of studies excluded because of deficient data and increasing the number of patients available for analysis. The quality of the majority of the studies included in this meta-analysis is considered low due to factors such as poor study design, inadequate sample size, selective reporting, or high attrition bias (Table 3, 4). An ideal clinical trial to evaluate the impact of varicocele repair on male fertility outcomes would be to randomize a group of male with subfertility to varicocele repair or sham surgery and follow their outcomes over time. However, many ethical concerns surround such an approach and prevent its implementation. This explains the paucity of high-quality studies on the effects of varicocele repair and male fertility potential. In this regard, a meta-analysis of low-risk-of-bias RCTs would give the best QoE on the impact of varicocele repair on sperm parameters. However, since high-quality RCTs are lacking, the very large number of subjects available in the present analysis helps mitigate the limitation of a before-after analysis (Fig. 2).

## CONCLUSIONS

The current meta-analysis is the largest one to date. The significant improvement seen in almost all semen parameters, including semen volume, sperm concentration, total sperm count, total motile sperm count, progressive sperm motility, total sperm motility, and sperm morphology, provides strong support for the role of varicocele repair in infertile male with clinical varicoceles.

### Conflict of Interest

The authors have nothing to disclose.

### Funding

None.

## Acknowledgements

Authors wish to thank the members of the Global Andrology Forum for their support.

## Author Contribution

Conceptualization: AA. Data curation: RC, FB. Formal analysis: RH, AMH. Methodology: AA, Shah R, RC, AMH. Project administration: AA, Shah R, RC. Supervision: AA, Shah R. Writing – original draft: RC, FB, Saleh R, MG, AR, PK, TT, EK, GC, DD, NA, SK, AC, RH, AMH, GS, BH, MD, MB, SD, MF, NG, RK, RSK, KK, TAAAMH. Writing – review & editing: All authors.

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