Azoospermia is defined as the complete absence of sperm from the ejaculate without implying an underlying cause. This condition is present in approximately 1% of all men and up to 15% of infertile men [285, 286]. Azoospermia may result from mechanical blockage occurring anywhere along the reproductive tract, including the vas deferens, epididymis, and ejaculatory duct, but most often it is associated with a spectrum of various severe and untreatable conditions causing an intrinsic testicular impairment, which is termed non-obstructive azoospermia (NOA) [287].

Varicocele is found in 5% of men with NOA, but its absolute impact on the azoospermic status is still unknown [230]. The advent of assisted reproductive technologies (ART), particularly intracytoplasmic sperm injection (ICSI), has reintroduced the awareness about varicocele with NOA, as improvement in testicular function to obtain viable sperm for ART may be critical for infertile men with NOA.

Genetic evaluation including karyotype and Y chromosome mapping are crucial in the work-up of men with varicocele and azoospermia. Microdeletions of the Y chromosome (YCMD) can be identified in up to 18% of these men [286]. Molecular diagnosis and subtyping of Y-chromosome microdeletions (YCMD) have been useful markers not only to detect the males in whom NOA is caused by YCMD, but also to counsel the affected patients about their chances of sperm retrieval success. Furthermore, the affected patients should be aware of abnormalities so that they can obtain genetic counseling in order to quantify their risk of transmitting them to their offspring. Finding a microdeletion within the AZFa or AZFb regions practically implies that the chances of SR success are virtually non-existent. Therefore, it would be unreliable to recommend varicocele repair in such cases [288, 289].

A meta-analysis was conducted to assess the impact of surgical repair in 233 men with clinical varicocele and NOA [231]. At an average follow-up of 13 months, motile spermatozoa were detected in 39% of subjects and pregnancy was successfully attained in approximately 26% of men with sperm in the ejaculate, 60% unassisted (14 cases), and 40% with in vitro fertilization techniques. Postoperative mean sperm density and percent sperm motility were 1.6 million and 20%, respectively. Testicular histopathology was the single predictor of success. Success rates in patients with maturation arrest (42.1%) or hypospermatogenesis (HS) (54.5%) were...
Varicocele and Azoospermia significantly higher than in those with Sertoli-cell-only (SCO) (11.3%, \( p<0.001 \) in both groups). These results indicated that biopsy-proven hypospermatogenesis and maturation arrest (MA) were significantly more likely to correlate with finding sperm in the ejaculate than Sertoli-cell only (odds ratio 9.4; CI 95% 3.2–27.3) [231]. Since a gradual decline in spermatogenesis and return to azoospermia have been reported in up to 55.5% of patients 1 year after surgery, semen cryopreservation may be recommended following initial improvement after surgery because the beneficial effects of varicocele repair in the recovery of spermatogenesis may be only temporary [290].

The aforementioned data was corroborated by another meta-analysis compiling five studies and 90 patients with varicocele and NOA. Testis biopsy revealed hypospermatogenesis in 30 out of 90 men (33%), maturation arrest in 26 out of 90 (29%) and Sertoli-cell-only in 34 out of 90 (38%) [291]. The successful appearance of spermatozoa in the ejaculate after varicocele repair was significantly higher in men classified as having hypospermatogenesis or maturation arrest than those with Sertoli-cell-only (18 out of 30 vs one out of 34, \( p=0.001 \); 12 out of 26 vs one out of 34, \( p=0.002 \), respectively. The success rate of varicocele repair did not differ when hypospermatogenesis was compared with maturation arrest (18 out of 30 vs 12 out of 26, \( p=0.65 \) [291]. Furthermore, the group of men with hypospermatogenesis or maturation arrest at spermatid stage achieved higher success (13 out of 26) after surgery compared with the group of men with maturation arrest at early spermatocyte or Sertoli cell only (0 out of 18). The difference was statistically significant (\( p=0.001 \) [291].

The informative nature of the histopathology results in deciding to pursue a varicocele repair would allow for evidence? that about 50% of the men with NOA avoided an unnecessary varicocelectomy. However, the risks of performing a diagnostic testicular biopsy with the sole purpose of histopathology evaluation may outweigh the benefits, as biopsies could remove focal areas of spermatogenesis that will jeopardize future retrieval attempts. Whenever a biopsy is carried out, caution should be taken to excise minimal tissue. Examination of wet specimens for the presence of sperm would allow cryopreservation to be offered. In addition, a meticulous histopathology evaluation would allow to differentiate pure SCO pattern from the cases in which focal spermatogenesis existed.

Although motile ejaculated sperm is preferred for ICSI, persistent azoospermia after varicocele repair is still a potential problem and surgical sperm retrieval (SR) before ICSI will be inevitable for many individuals [290]. Nevertheless, since higher fertilization rates and better ICSI outcomes when fresh, motile, ejaculated sperm are used compared with sperm provided by testicular biopsy or microsurgical testicular sperm extraction, contemplating varicocele repair to help with the appearance of viable sperm in the ejaculates of men with NOA remains an attractive option [292].

As far as sperm retrieval is concerned, comparative studies involving varicocele-treated and untreated individuals are scarce. In one study, SR rates were similar (60%) in azoospermic men who underwent varicocele repair versus those who did not [293]. Nevertheless, others suggested a beneficial role of intervention. Inci et al. [276] studying a group of 96 men observed that SR success was 2.6 fold higher in
treated compared with untreated men (53 vs. 30%, OR: 2.63, 95% CI: 1.05–6.60; \( p=0.03 \)). In another study involving 66 men, Haydardedeoglu et al. [294] reported higher SR success in men who had varicocele repair prior to SR (61%) compared with untreated men (38%; \( p<0.01 \)).

Although an argument can be made that a control group would remain azoospermic, it is not rare to observe that NOA men occasionally ejaculate small quantities of motile sperm even without any intervention.

In conclusion, the limited available evidence precludes a firm conclusion about the role of varicocele and the benefits of its repair in men with NOA. Until a consensus is reached on the optimal management approach to infertile men with NOA and varicocele, it seems reliable to offer varicocele repair to men with hypospermatogenesis and maturation arrest provided YCMD involving the subregions AZFa and AZFb have been excluded. Men with SCO pattern and those who failed to have sperm in their ejaculates after varicocele repair can be counseled to pursue surgical sperm retrieval. Along these lines, it has been our routine to offer microsurgical repair of varicoceles before sperm retrieval, particularly to young men (<35 years) with large bilateral varicoceles (Grades 2 and 3) after proper counseling [273].

Key Points

• Varicocele is found in 5% of men with non-obstructive azoospermia.
• As crucial part of in the work-up of azoospermic men with varicocele, genetic evaluation is pre-requisite including karyotype and Y chromosome mapping. Genetic testing and counseling is important to select the patients who might benefit from varicocele repair, and raise parental awareness about possibility of transmission of any genetic alteration to biological offspring.
• Microdeletions of the Y chromosome (YCMD) can be identified in up to 18% of these men. YCMD within the AZFa or AZFb subregions virtually implies that there are no chances of sperm retrieval success. Therefore, it would be practically unwise to recommend varicocele repair in such cases.
• Testicular histopathology was the single main determinant for successful appearance of the spermatozoa in the ejaculate and for successful pregnancy outcomes.
• A firm recommendation about the role of varicocele repair in men with NOA is still to be determined. There is critical need for randomized controlled trials to examine the potential advantages of varicocele repair in men with NOA.