



## **Evidence Review:**

# **Surgical sperm retrieval for male infertility**

**NHS England**

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First published: January 2016

Updated: N/A

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## 1. Introduction

Surgical sperm retrieval is the retrieval of sperm for fertilisation from the epididymis or testicles to assist conception for couples where the male partner suffers from azoospermia. The retrieved sperm is used immediately for fertilisation or stored for future fertility treatment. This enables men to father their own genetic offspring through intra-cytoplasmic sperm injection (ICSI) fertility treatment. The alternative would be to use donor sperm or to adopt.

Surgical sperm retrieval includes the following techniques:

- Percutaneous epididymal sperm aspiration (PESA)
- Microsurgical epididymal sperm aspiration (MESA)
- Testicular sperm aspiration (TESA), also described as testicular fine needle aspiration (TEFNA)
- Testicular sperm extraction (TESE)
- Microdissection testicular exploration and sperm extraction (mTESE)

In obstructive azoospermia, sperm can usually be obtained from the epididymis (PESA or MESA) and from the testis (TESA or TESE or mTESE).

In non-obstructive azoospermia, sperm needs to be obtained directly from the testis by (TESA or TESE or mTESE)

Historically, in infertile couples where the female is fertile but the male is infertile, the availability of treatment for men has been geographically variable. This can result in inequality where infertile females can undergo IVF/ICSI but infertile males with a fertile partner may be unable to access therapy.

## 2. Summary of results

### **Evidence review summary for surgical sperm retrieval techniques for non-obstructive azoospermia (including Klinefelter Syndrome and Y chromosome deletions)**

In summary, and consistent with NICE's findings in 2013, the best method of extracting spermatozoa from the testicular tissue in non-obstructive azoospermia is uncertain including a lack of evidence regarding the relative merits of TESA and TESE using small (5mm), multiple or large (10-15mm) biopsies. Their evidence review found that compared with TESE, TESA has a reduced rate of sperm recovery but is less invasive (level 3 evidence). (NICE 2013)

A 2008 Cochrane review (Cochrane Database Systematic Review, 2008) on techniques for surgical retrieval of sperm for azoospermic men undergoing ICSI concluded there was insufficient evidence to recommend any specific sperm retrieval technique. The review was restricted to RCTs and results was based on two RCTs studying microsurgical epididymal sperm aspiration (MESA) and testicular aspiration techniques (TESA/TESE/mTESE).

A review of published studies up to October 2015 found some evidence that mTESE is better than TESE, but there is a lack of data on important clinical measures such as long term complication rates, viability of the retrieved sperm and successful pregnancy rates. The generalisability of the results are limited due to the lack of good quality studies in the review (level of evidence SIGN 2- to 3).

### **Comparison of sperm retrieval success rates of microsurgical TESE (mTESE) v conventional TESE (TESE) in men with non-obstructive azoospermia**

There are no new randomised controlled trials or good quality observational studies comparing TESE with mTESE since the last Cochrane update in 2008. The evidence comparing TESE and mTESE in men with non-obstructive azoospermia is available from three systematic reviews (Donoso et al., 2007, Deruyver et al., 2014 and Bernie et al., 2015) which are predominantly based on retrospective or prospective case series (SIGN level of evidence 2- to 3). Of the three reviews, the latest systematic review by Bernie et al. (2015) provides the most comprehensive evidence available so far comparing TESE and mTESE. This review by Bernie et al. (2015) includes the majority of studies included in the previous two reviews by Donoso et al. (2007) and Deruyver et al. (2014). The systematic review by Bernie et al. (2015) is presented with a good study design, inclusion and

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exclusion criteria and sound methodology for data synthesis and meta-analysis. The results of this review show that mTESE was 1.5 times more likely (95% CI 1.4–1.6) to result in successful sperm retrieval compared with TESE in men with non-obstructive azoospermia.

Donoso et al. (2007) found that mTESE performs better than TESE only in patients with Sertoli-cell-only syndrome where tubules containing active foci of spermatogenesis can be identified, but this could not be verified from the systematic review by Bernie et al. (2015). The available evidence on complication rates suggests that mTESE is safer than TESE, with fewer complications including haematoma fibrosis, and testicular atrophy (Donoso et al., 2007), however the rates varied from study to study. There is no data from any of the three systematic reviews on the viability of retrieved sperm and the information on pregnancy rates or live birth is inadequately presented to draw any conclusions.

### **Successful sperm harvesting and retrieval in men with Klinefelter syndrome**

Based on one systematic review by Mehta et al. (2012), the average overall sperm retrieval rate in patients with Klinefelter syndrome was 51%, with a range of 28%–69% at various centres, using different surgical techniques. mTESE had higher retrieval rates compared to TESE (61% vs.47%). Studies varied in their conclusions as to predictors of sperm retrieval. Positive predictors included younger age and pre-operative T levels close to or within the normal range, either at baseline or with hormone treatment (aromatase inhibitors, clomiphene citrate, or hCG). Serum LH, FSH levels and testicular volume, were not predictive of testicular spermatogenic function. Results for pre-treatment testicular histology as a predictor was variable, with some showing a positive relationship and others showing no relationship. Due to the lack of meta-analysis in the systematic review and poor quality of studies identified in the review (all were retrospective case series with no randomisation or control group with heterogeneity of laboratory methods) the generalisability of these results are limited.

### **Y Chromosomal deletions including microdeletions of Y chromosome, including in the AZFa, AZFb, AZFc and combined-region deletions**

Patients with deletions in the AZFc region, the most common microdeletion seen, are often able to have successful sperm retrieval with mTESE. In two retrospective studies with more than 100 patients with microdeletion (Stahl et al., 2010 and Park et al., 2013) the sperm retrieval rate in patients AZFc microdeletion ranged from 54.1% to 71.4% but that there was no sperm retrieved in any men with AZFa and AZFb. In patients with AZFb + c, the study by Park et al. (2013) showed a success rate of 7.1%.

Additionally, there are good clinical outcomes of fertilisation in people with AZFc deletions. A Chinese study of 143 people with Y chromosome AZFc microdeletion in ICSI cycles (Liu et al. 2013), showed the clinical success rates (transferred embryos, good embryo rates, implantation rates, clinical pregnancy rates, ectopic pregnancy rates, miscarriage rates, preterm birth rates, new-born height and weight, and birth defects) in the AZFc deletion group was similar to those with normal Y chromosomes in ICSI ( $p>0.05$ ).

In summary, there is consistent evidence that patients with deletions in the AZFc region, the most common microdeletion seen, have higher rates of successful sperm retrieval with mTESE compared to patients with in AZFa, AZFb or combined-region deletions.

### **Evidence review summary for surgical sperm retrieval techniques for obstructive azoospermia**

In summary, there is insufficient evidence to recommend one surgical sperm retrieval technique over another for men with obstructive azoospermia.

According to the NICE Clinical Guideline (2013) there is no consistent relationship between the type of surgical sperm retrieval and successful pregnancy rates and they found that epididymal and testicular spermatozoa yield similar fertilisation, cleavage and ongoing pregnancy rates using ICSI (evidence level 3).

The NICE review (2013) suggests that when spermatozoa cannot be recovered by one technique another one can be employed, for example, TESE after MESA. Spermatozoa obtained from testicular aspiration can be successful in achieving fertilisation and pregnancies for couples in whom epididymal aspiration failed.

### **Clinical effectiveness of PESA, TESA, MESA, cTESE and mTESE in men with obstructive azoospermia**

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Obstructive azoospermia is characterised by normal testicular function (with normal sperm production), the absence of spermatozoa in semen, and genital tract obstruction. Obstructive azoospermia accounts for approximately 15%-20% of all azoospermia cases. Obstructive azoospermia can be congenital or acquired and causes can be divided into intra-testicular, epididymal, vasal, and ejaculatory duct obstruction. Post-vasectomy obstruction and congenital bilateral absence of the vas deferens (CBAVD) are the most common causes of Obstructive azoospermia.

Testicular or epididymal sperm retrieval (combined with ICSI) is an option for men with obstructive azoospermia. The evidence of effectiveness for the above methods comes from two systematic reviews (Cochrane 2009 and NICE evidence review 2013) and a number of retrospective case series.

The Cochrane review (Cochrane review, 2009) included two RCTs. The first RCT (Yamamoto et al., 1996) compared microsurgical epididymal sperm aspiration (MESA) versus micropuncture with perivascular nerve stimulation for patients with surgically irreparable vasal obstruction (CBAVD and failed vasovasostomy). This study reported lower pregnancy (OR 0.19, 95% CI 0.04 to 0.83) and fertilisation rates (OR 0.16, 95% CI 0.05 to 0.48) in the MESA group (evidence level 1a).

Another RCT from Israel (Belenky, 2001) compared percutaneous testicular aspiration with ultrasound guidance (TESA with US) versus percutaneous testicular aspiration without ultrasound guidance (TESA) in 39 participants. There was no statistically significant difference between the two groups. TESA with US in pregnancy in three out of sixteen participants compared with four out of 23 participants (odds ratio 1.10, 95% CI 0.21 to 5.74).

The NICE review (2013) reported very low failure rates for surgical sperm retrieval methods:

- MESA: 1.7% of men (1/59) - 22% of men (2/9),
- PESA: 5% in men with failed reversed vasectomy, 11% in men with CBAVD and 15.8% to 17% of initiated cycles,
- TESA: 0%.

These methods were found to be effective in men with CBAVD and in those with failed reversal of vasectomy, the main causes of obstructive azoospermia.

Bernie et al (2011) reported the following outcome rates by various techniques:

- MESA: performed under general or regional anaesthesia with a sperm retrieval rate of 95%–100% of cases. Yield- 15–95\*10<sup>6</sup> total sperm with 15%–42% total motility, cryopreservation possible in 98%–100% of cases with an average of 5.3–7.6 vials per patient.
- PESA: performed under local anaesthesia with a sperm retrieval rate of 80%–100%. Yield-Thousands to millions of sperm with variable motility (poorly reported in most studies), cryopreservation possible in 43%–96% of cases.
- TESA (Testicular fine needle aspiration): performed under local anaesthesia with a sperm retrieval rate of 52%–100%. Yield-Hundreds of thousands to millions of sperm with variable motility (poorly reported in most studies), cryopreservation possible in 38% of cases in one study.
- TESA (Testicular large needle aspiration): performed under local anaesthesia with a sperm retrieval rate of 98%–100%. Yield-Hundreds of thousands to millions of sperm with variable motility (poorly reported in most studies), cryopreservation possible in 100% of cases in one study.
- TESA (Testicular core needle biopsy): performed under local anaesthesia with a sperm retrieval of 82%–100%. Yield-Hundreds of thousands to millions of sperm with variable motility (poorly reported in most studies), often sufficient for cryopreservation (poorly reported).
- TESE: performed under local or general anaesthesia with a sperm retrieval rate of 100%. Yield-Hundreds of thousands to millions of sperm in most cases (poorly reported in most studies), usually sufficient for cryopreservation (poorly reported).
- mTESE: performed under local or general anaesthesia with sperm retrieval rate of 100%. Yield-Hundreds of thousands to millions of sperm in most cases (poorly reported in most studies), usually sufficient for cryopreservation (poorly reported).

A study by Kovac et al. (2013), of 51 men with obstructive azoospermia undergoing PESA plus ICSI reported 100% success rate for sperm retrieval, 78% fertilization and 49% pregnancy rate. Another study by Yafi et al. (2013) of 255 men with obstructive azoospermia undergoing PESA for sperm retrieval reported a success rate of 77% and suggested that younger age was positively related to successful retrieval of motile sperm.

A recent study by van Wely et al. (2015) of 374 patients comparing MESA-ICSI (280) with TESE-ICSI (94)

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reported a significantly better outcome from MESA-ICSI, including the amount of sperm extracted ( $p < 0.001$ ), higher proportion of frozen cycles (60 vs 15%,  $p < 0.001$ ), higher live birth rates (39 vs 24%,  $p = 0.001$ ) and higher clinical and ongoing pregnancy rates (47 vs 39%).

### **Evidence review summary for other questions considered by the review**

#### **Predictive factors for successful sperm retrieval in non-obstructive azoospermia (histology, FSH, inhibin, testosterone, testicular volume)**

The evidence for predictive factors for successful surgical sperm extraction comes from a number of retrospective and prospective studies, one review article (Bernie et al., 2013) and one systematic review (Yang et al., 2015), which evaluates FSH as a predictor for sperm retrieval in non-obstructive azoospermia. Based on the review by Bernie et al. (2013), the only good predictor of successful retrieval was testicular histology but having to perform a separate surgical procedure for diagnosis limits its use, as a simultaneous sperm retrieval can be undertaken. There is no clear relationship between successful sperm retrieval and serum FSH or serum inhibin –B levels, or testicular volume. Models to calculate the predictivity rates with data crossed with other parameters (age, duration of fertility and hormonal (LH, testosterone, prolactin)) have not shown to be useful in predicting successful sperm extraction.

In a study by Hussein et al. (2013) the rate of successful sperm extraction using mTESE was compared in two groups of men with azoospermia, one study (496 males) receiving clomiphene citrate and another group of (119 males) with no clomiphene citrate treatment. Patients receiving clomiphene citrate had higher rates of successful sperm retrieval compared to those who did not receive medication (57% vs 34%). However, due to the lack of randomisation, lack of information on baseline characteristics of the two groups and possible bias due to patient selection methods, the results cannot be generalised.

In summary, there is no clear relationship between successful sperm retrieval and serum FSH or serum inhibin –B levels, or testicular volume. The only good predictor of successful retrieval was testicular histology but the requirement of a separate surgical procedure for diagnosis limits its use.

#### **Patients with varicoceles and non-obstructive azoospermia**

Evidence on the impact of surgical repair of a varicocele in patients with non-obstructive azoospermia comes from a meta-analysis of 11 studies with 233 men with clinical varicocele and non-obstructive azoospermia (Weedin et al. 2010). At a mean follow up of 13 months, motile sperm was found in 39% of study subjects; pregnancy was achieved in approximately 26% of men with sperm in the ejaculate (60% unassisted and 40% assisted with IVF).

The probability of successful varicocele repair was significantly greater for patients with azoospermia due to hypospermatogenesis or late maturation arrest than for those with Sertoli-Cell-Only (Odds Ratio 9.4; 95% CI 3.2-27.3).

#### **Success rates of repeat sperm retrieval surgery in men with non-obstructive azoospermia**

The evidence for success rates of repeat sperm retrieval surgery in men with non-obstructive azoospermia is based on a very small number of retrospective case series with varying patient selection criteria and methodologies. The success rate of repeat TESE varied from 30% (Haimov-Kochman et al, 2009) to 41.6% (Vernaev et al, 2006) in the first repeat attempt and the success rate increased to 100% for two patients with six attempts (Vernaev et al, 2006), there are limitations of this evidence as only 2 out of 628 patients in the study reached six attempts, hence it is difficult to generalise.

One retrospective case series of repeat mTESE (Ramasamy et al, 2011) showed a success rate of 82%. The study identified lower follicle-stimulating hormone level and larger testicular volume to have a predictive value in determining the success of a second attempt. The findings of the study are limited by its retrospective, nonrandomized, non-controlled nature.

In summary, there is low level evidence from retrospective case series that the cumulative success rate of repeat sperm retrieval increases with increasing numbers of attempts and is higher in males who have had a previous successful attempt. The results are not substantiated by other studies, hence the replicability of these results in other patients or settings is limited.

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### **Comparison of psychosocial impact of men with successful and unsuccessful surgical sperm retrieval**

No evidence was identified from the literature search to compare the psychosocial impact of men with successful and unsuccessful surgical sperm retrieval.

### **Congenital disorders in live births following ICSI using sperm from TESE or mTESE in non-obstructive azoospermic men**

No evidence was identified from the literature search to compare the risk of congenital disorders in live births following ICSI using sperm from TESE or mTESE in non-obstructive azoospermic men.

### **Risk of multiple pregnancy following ICSI using surgical sperm retrieval**

No evidence was identified from the literature search to compare the risk of multiple pregnancy following ICSI using surgical sperm retrieval.

## **3. Research questions**

1. Comparison of sperm retrieval success rates of microsurgical TESE (mTESE) v conventional TESE
2. Successful sperm harvesting and retrieval in men with Klinefelter's syndrome and Y chromosomal deletions
3. Success rates of repeat sperm retrieval surgery in men with non obstructive azoospermia
4. Proportion of men with non-obstructive azoospermia offered a surgical sperm retrieval
5. Predictive factors for successful sperm retrieval in non-obstructive azoospermia
6. Effects of treating a varicocele prior to surgical sperm retrieval in non-obstructive azoospermia
7. Relationship between testosterone levels and successful surgical sperm retrieval in non-obstructive azoospermia
8. Comparison of psychosocial impact of men with successful and unsuccessful surgical sperm retrieval
9. Congenital disorders in live births following ICSI using sperm from TESE or mTESE in non-obstructive azoospermic men
10. Risk of multiple pregnancy following ICSI using surgical sperm retrieval
11. Quality of life issues in couples undergoing ICSI using donor sperm
12. What is the clinical effectiveness of PESA, TESA, MESA, cTESE and mTESE, including repeat procedures, in men with obstructive azoospermia?

## **4. Methodology**

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

## **5. Results**

A detailed breakdown of the evidence is included in the Appendix.



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Appendix

Grade of evidence	Study design and intervention			Outcomes					Reference	Other		
	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Second-ary Outcome	Second-ary Result	Reference	Complications noted	Benefits noted	Comments
1-	Systematic review	1,890 patients	Surgical sperm extraction	Clinical effectiveness of the intervention	Sperm retrieval (SR) authors report that the definition of successful SR used by the studies was not explicitly defined in the articles, but have assumed that a single sperm that could be either preserved or used for IVF/CSI constituted as a success.	cTESE vs micro-TESE, the unadjusted SR of 35% for cTESE (95% CI 30%–40%; t2 ¼ 0.02; P=.28; I2 ¼ 19%) and 52% for micro-TESE (95% CI 47%–58%; t2¼0.04; P¼.07; I2¼48. Micro-TESE was 1.5 times more likely (95% CI 1.4–1.6) to result in successful SR as compared with cTESE. cTESE vs TESA, the unadjusted SR was 56% for cTESE (95% CI 50%–61%; t2 ¼ 0.02; P¼.20 I2 ¼ 31%) and 28% for TESA (95% CI 19%–39%; t2 ¼ 0.27; P<.01; I2 ¼ 80%). Therefore, performance of cTESE was 2.0 times more likely (95% CI 1.8–2.2) to result in successful SR as compared with TESA. Authors in discussion recognise that these results are based on small number of retrospective and prospective studies with selection bias and confounders including heterogeneity of patients in different studies, varying laboratory techniques, differing surgeon skill levels.	None		Bernie, Aaron M.; Mata, Douglas A.; Ramasamy, Ranjith; Schlegel, Peter N.. Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis. Fertil. Steril.. 2015,	None evaluated/studied	No evaluation of pregnancy rate, live birth, patient satisfaction, quality of life	<p>This is a systematic review and meta-analysis of comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for non-obstructive azoospermia. The review has a good study design including a priori protocol with study design, search strategy, inclusion and exclusion criteria, primary outcomes, statistical methods, and assessment for bias in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Literature search included English-language studies reporting on outcomes of TESA or TESE for SR in men with NOA published between 1988 and 2015. Articles were identified through electronic search of MEDLINE, scanning the reference lists of identified articles, and correspondence with study investigators. Meta-analysis was performed using a random effects model. The consistency of findings across studies was assessed using Cochrane's Q test and the I2 statistic. Publication bias was assessed by funnel plot. Statistical significance was defined as a two-tailed P value of &lt;.05. Analyses were performed using R version 3.1.2.</p> <p>Summary of study outcomes according to research questions:                      Comparison of sperm retrieval success rates of microsurgical TESE (mTESE) v conventional TESE: Direct comparison of cTESE to micro-TESE, the unadjusted SR was 35% for cTESE (95% CI 30%–40%; t2 ¼ 0.02; P¼.28; I2 ¼ 19%) and 52% for micro-TESE (95% CI 47%–58%; t2¼0.04; P¼.07; I2¼48%) (Fig. 1A). Overall, the performance of micro-TESE was 1.5 times more likely (95% CI 1.4–1.6) to result in successful SR as compared with cTESE. However the these are results are based on results on a small number of retrospective and prospective studies of low quality study design with selection bias and unadjusted for confounders including heterogeneity of patients in different studies, varying laboratory techniques, differing surgeon skill levels.</p> <p>Research questions that can't be answered:                      Successful sperm harvesting and retrieval in men with Klinefelter's syndrome and Y chromosomal deletions.                      Success rates of repeat sperm retrieval surgery in men with non obstructive azoospermia.                      Proportion of men with non-obstructive azoospermia offered a surgical sperm retrieval.                      Predictive factors for successful sperm retrieval in non-obstructive azoospermia.                      Effects of treating a varicocele prior to surgical sperm retrieval in non-obstructive azoospermia.                      Relationship between testosterone levels and successful surgical sperm retrieval in non-obstructive azoospermia.                      Comparison of psychosocial impact of men with successful and unsuccessful surgical sperm retrieval.                      Congenital disorders in live births following ICSI using sperm from TESE or mTESE in non-obstructive azoospermia men.                      Risk of multiple pregnancy following ICSI using surgical sperm retrieval.                      Quality of life issues in couples undergoing is using donor sperm.</p>

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1+	Systematic review	1350	mTESE, cTESE	Clinical effectiveness of the intervention	Summary receiver operation. characteristics (SROC) and the area under ROC curve (AUC) of FSH's diagnostic value as a predictor for SRR in patients with NOA before TESE/MESE	Pooled analysis showed that the area under ROC curve of FSH was $0.72 \pm 0.04$ suggesting FSH had moderate value in independently predicating SRR in men with NOA (area under curve $>0.7$ ). Meta regression analyses showed that FSH had more diagnostic value with patients in East Asia and with younger patients.	None		Yang, Qi; Huang, Yan-Ping; Wang, Hong-Xiang; Hu, Kai; Wang, Yi-Xin; Huang, Yi-Ran; Chen, Bin. Follicle-stimulating hormone as a predictor for sperm retrieval rate in patients with nonobstructive azoospermia: a systematic review and meta-analysis. Asian J. Androl.. 2015,	None studied	As in primary outcome results	This is a well designed systematic review with meta-analysis of published data to estimate diagnostic value of FSH as a predictor for sperm retrieval rate (SRR) in patients with NOA before testicular sperm retrieval. Statistical analysis included calculation of specificity and sensitivity, with a 95% confidence interval (CI). Continuous outcomes are presented as SROC, and qualitatively described as AUC. The chi-square test and I2 statistic were used to analyse the heterogeneity in the results. Meta regression and stratified analyses on year of publication, region, patients' average age and sample size was performed to identify the source of heterogeneity. All the studies included in the study are either retrospective or prospective case series (level of evidence=2) with no randomisation or control group hence limiting the generalisability of the findings. The results showed FSH had moderate value in independently predicting the SRR in men NOA.
2+	Multi study	612 patients with azoospermia	mTESE in 496 who received clomiphene citrate, hCG and hMG	Clinical effectiveness of the intervention	Successful sperm retrieval	For the 442 patients who remained azoospermic after treatment, successful sperm retrieval was significantly higher (57%) compared with the control group (33.6%)	None		Hussein, Alayman; Ozgok, Yasar; Ross, Lawrence; Rao, Pravin; Niederberger, Craig. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. BJU Int.. 2013,	None mentioned	Increases sperm retrieval with mTESE in azospermic patients treated with clomiphene citrate, hCG and hMG	This is prospective study of 612 patients with azoospermia compared the successful sperm retrieval in clomiphene treated patients with untreated patients. Rate of success sperm retrieval with mTESE was higher patients receiving in patients who received clomiphene citrate, hCG and hMG than who did not. The study has limitations in that the patients selection for interventions was not random and there is no baselines characteristics for the two groups is not described. Therefore the result of the study can not be generalised.

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2+	Systematic review	497 patients	Hormonal treatment, surgical sperm retrieval including cTESE and mTESE, ICSI	Clinical effectiveness of the intervention	Surgical sperm retrieval in the setting of hormonal treatment	The average overall sperm retrieval rate was 51%, with a range of 28%–69% at various centres, using different surgical techniques. mTESE had higher retrieval rates compared to cTESE (61% vs.47%). Studies varied in their conclusions as to predictors of sperm retrieval, positive predictors included young age and preoperative T levels close to or within the normal range, either at baseline or with HT (aromatase inhibitors, clomiphene citrate [CC], or chg.). Serum LH, FSH levels testicular volume, were not predictive of testicular spermatogenic function. Results for Pre-treatment testicular histology as a predictor was variable; some showing positive relation with others showing no relation.	None		Mehta, Akanksha; Paduch, Darius A.. Klinefelter syndrome: an argument for early aggressive hormonal and fertility management. Fertil. Steril. 2012,	None reported		This is a systematic review published data on sperm retrieval in klinefelter with a good description of search strategy, inclusion and exclusion criteria but doesn't include synthesis of data using met analysis. All the studies included in the study are either retrospective or prospective case series with no randomisation or control group hence limiting the generalisability of the findings. Fertility outcome which is a useful outcome was not reported for all the studies, where reported the measures used varied from delivery of live child to fertilisation of egg.
2+	Systematic review	98 participants (59 and 39 patients)	Surgical sperm-extraction techniques: microsurgical epididymal sperm aspiration (MESA); Percutaneous epididymal sperm aspiration (PESA); Testicular sperm extraction (TESE) or testicular biopsy; Testicular sperm aspiration (TESA) or testicular fine needle aspiration (TEFNA)	Clinical effectiveness of the intervention	Primary outcomes: Birth rate - live birth per couple; Pregnancy rate per couple - number of couples achieving a clinical pregnancy (which should be confirmed by ultrasound) divided by the number of couples; Adverse effects associated with sperm-retrieval technique (e.g. haematoma, infection, severe bruising, pain)	Two trials involving 98 men were included. The first small RCT had 59 participants and compared two epididymal techniques. The trial gave limited evidence that microsurgical epididymal sperm aspiration (MESA) achieved a significantly lower pregnancy rate (one pregnancy in 29 procedures compared with seven pregnancies in 30 procedures; OR 0.19, 95% CI 0.04 to 0.83) and fertilisation rate (OR 0.16, 95% CI 0.05 to 0.48) than the micropuncture with perivascular nerve stimulation technique. The other RCT comparing two testicular aspiration techniques (TSA) in 39 participants gave no statistically significant evidence for the superiority of the ultrasound guided technique compared to the aspiration technique without ultrasound. TSA with ultrasound resulted in pregnancy in three out of 16 participants compared with four out of 23 participants (OR 1.10, 95% CI 0.21 to 5.74).	Pregnancy rate per cycle; Fertilisation rate; Implantation rate; Sperm parameters of tissue obtained from the surgical retrieval procedure, including fluid volume, sperm motility, sperm morphology, sperm density (however measured by each trial); Multiple pregnancy rate); Miscarriage rate (per intra-uterine pregnancy and/or per woman); Fetal abnormalities (any reported either in utero or after birth)	0	Van Peperstraten, A.; Proctor, M. L.; Johnson, N. P.; Philipson, G.. Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia. Cochrane Database Syst Rev. 2008,	None included in the results of systematic review	As in primary outcome measure	The Cochrane reviews considered the gold standards in systematic review is presented with clear description of search methodology, inclusion and exclusion criteria, statistical methods for assessing the quality of studies. The review found only two studies which met the criteria. Other studies were all either case series and cohort studies with bias. The authors conclude that "there is insufficient evidence to recommend any specific sperm retrieval technique for azoospermic men undergoing ICSI". In the absence of evidence to support more invasive more technically difficult methods, the review authors recommend the least invasive and simplest technique available. Further randomised trials are warranted, preferably multi-centred trials. The classification of azoospermia as obstructive and non-obstructive appears to be relevant to a successful clinical outcome and a distinction according to the cause of azoospermia is important for future clinical trials.

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2+	Systematic review	460 patients with mTESE	mTESE	Clinical effectiveness of the intervention	Sperm retrieval rate	The mean SRR for cTESE was 49.5% (95% CI 49.0–49.9). TESE with multiple biopsies results in a higher SRR than FNA especially in cases of Sertoli-cell-only (SCO) syndrome and maturation arrest. mTESE performs better than conventional TESE only in cases of SCO where tubules containing active focus of spermatogenesis can be identified.. mTESE had lower complication rates	Complications and live birth rates	could not be established due to lack of information from studies included	Donoso, P.; Tournaie, H.; Devroey, P.. Which is the best sperm retrieval technique for non-obstructive azoospermia? A systematic review. Hum. Reprod. Update. 2007,	Complication including haematoma fibrosis and testicular atrophy, the rates varied from study to study but generally mTESE has fewer complications than cTESE	The study establishes benefits of mTESE in SCO with azoospermia	This is a systematic review of published data on comparing cTESE with mTESE and FNA for non-obstructive azoospermia. The methodology doesn't include synthesis of data using meta-analysis. All the studies included in the study are either retrospective or prospective case series with randomisation or control group hence limiting the generalisability of the findings. Fertility outcome including pregnancy rate and live birth rate which are useful outcome could not be established. The generalisability of results of this study are seriously limited by the quality of studies included
2+	Other	Variable	mTESE	Clinical effectiveness of the intervention	Sperm retraction rate	There is no clear relation between successful sperm retrieval and serum FSH or serum inhibin –B levels, or testicular volume.	Not included		Aaron M Bernie, Ranjith Ramasamy and Peter N Schlegel. Predictive factors of successful microdissection testicular sperm extraction. Basic and Clinical Andrology . 2013,	None included	As per primary outcome	This is a narrative review of factors predicting successful mTESE testicular sperm extraction in non obstructive azoospermia with no systematic analysis or meta-analysis of data. However provided good over view of all that factors that influence the outcome for mTESE with comprehensive list of studies from the past. generalisability of the results are limited due to poor study design.
0	Single study	874	mTESE	Clinical effectiveness of the intervention	Sperm retrieval rate by FSH and group with in Sertoli cell-only syndrome (SCOS)	Sperm retrieval rate (SRR) was 23.6% in men with presumed SCOS, and sperm retrieval rate in the group of men with FSH values >15.25% was 28.9% and was higher than the group of men with FSH ≤15.25 (11.8%).	None		Modarresi T, Hosseinifar H, Daliri Hampa A, Chehrizi M, Hosseini J, Farrahi F, Dadkhah F, Sabbaghian M, Sadighi Gilani MA. Predictive Factors of Successful Microdissection Testicular Sperm Extraction in Patients with Presumed Sertoli Cell-Only Syndrome . Vol 9, No 1, Apr-Jun 2015 . 2015,	None studied	Higher FSH leads to higher sperm retrieval rate	A retrospective case of men with azoospermia were compared for mTESE sperm retrieval rate by 2 FSH levels and rte in men SCOS. Main limitation of study are lack of randomisation, lack of clarity of patient selection criteria in two groups of FSH levels. Generalisability of results are limited due to above factors.

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2+	Single study	792	mTESE	Clinical effectiveness of the intervention	Sperm retrieval by FSH levels	Testicular sperm were successfully retrieved in 60% of the men. Sperm retrieval rates in the groups of men with FSH values 15–30, 31–45, and >45 IU/mL was 60%, 67%, and 60% respectively; this was higher than the group of men with FSH < 15 (51%). Of those men who had sperm retrieved, clinical pregnancy and live birth rates were similar in the four groups (46%, 50%, 52%, 46% and 38%, 45%, 44%, 36%, respectively).	None		Ranjith Ramasamy, M.D., <sup>a</sup> Kathleen Lin, M.D., <sup>b</sup> Lucinda Veeck Gosden, D.Sc., <sup>a</sup> Zev Rosenwaks, M.D., <sup>a</sup> Gianpiero D. Palermo, M.D., <sup>a</sup> and Peter N. Schlegel, M.D. <sup>a</sup> Center for Reproductive Medicine and Infertility, New York–Presbyterian Hospital, Weill Cornell Medical College, New York, . High serum FSH levels in men with nonobstructive azoospermia does not affect success of microdissection testicular sperm extraction. Fertil Steril . 2009,	None studied	As in primary outcome results	Retrospective case series of men with non obstructive azoospermia with clear case selection methods. Authors in the full paper suggest that after logistic regression patients 3 subgroups of FSH <15 had significantly higher success rate than the comparator group of FSH <15. However due to study design and lack of randomisation in patient selection methods generalisability of results are limited.
2-	Other	2890	mTESE	Clinical effectiveness of the intervention	Sperm retrieval take home babies	TESE was successful in 149 patients (53.2%). In a multivariate logistic regression analysis, only TTV, FSH and inhibin B were correlated with the TESE outcome.	None		F. Boitrelle1,*, G. Robin F. Marcelli, M. Albert, B. Leroy-Martin1, D. Dewailly, J.-M. Rigot3, and V. Mitchell1, . A predictive score for testicular sperm extraction quality and surgical ICSI outcome in non-obstructive azoospermia: a retrospective study. Human Reproduction, . 2011,	None included in the abstract	As per primary outcome results	A retrospective study in men with non-obstructive azoospermia demonstrating relation between TESE and total testicular volume, (TTV), FSH and inhibin B which were positively correlated. Generalisability of results are limited due to study design and lack of details on patient selection.

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2+	Systematic review	233	Varicocele repair	Clinical effectiveness of the intervention	Discovery of motile sperm in any semen analysis performed at least 3 months from postoperatively or spontaneously pregnancy	At a mean follow up of 13 months, motile sperm was found in 39% of subjects; pregnancy was achieved in approximately 26% of men with sperm in the ejaculate, 60% unassisted, and 40% with IVF. Postoperative mean sperm density and motility were 1.6 million and 20%, respectively. Histopathology was the only predictor of success. Biopsy-proven hypospermatogenesis (HS) and maturation arrest (MA) were significantly more likely to correlate with finding sperm in the ejaculate than Sertoli-cell only (SCO) (odds ratio 9.4; CI 95% 3.2–27.3).	None included		Weedin et al. Varicocele Repair in Patients With Nonobstructive Azoospermia: A Meta-Analysis . The journal of urology. 2010,	None included in the abstract	As per primary outcome results	This is a systematic review with meta-analysis of published data on effectiveness of varicocele operation in patients with non-obstructive azoospermia. Statistical analysis using SPSS® software included 2-tailed Fisher's exact test, the Fisher-Freeman-Halton test and the chi-square test to analyse categorical variables with p 0.05 considered statistically significant. All studies were retrospective case series. Bilateral repair was performed in 64.8% of patients. Motile sperm was found on postoperative semen analysis in 91 of 233 (39.1%) men, resulting in 14 (6%) spontaneous pregnancies and 10 pregnancies with the assistance of IVF. Patients with late maturation arrest had a higher probability of success (45.8%) than those with early maturation arrest (0%, p 0.007). The authors concluded that men with late maturation arrest and hypospermatogenesis have a higher probability of success and, therefore, histopathology should be considered before varicocele repair in men with non-obstructive azoospermia.
2-	Other	126 men	Repeat sperm retrieval	Clinical effectiveness of the intervention	Successful repeat attempt	testicular spermatozoa were successfully retrieved at 103 of 126 repeat attempts (82%). Men with a successful repeat attempt had lower follicle-stimulating hormone (mean $\pm$ SD 23.1 $\pm$ 12.4 vs 29.2 $\pm$ 12.8, p = 0.04) and larger testicular volume (mean 10 $\pm$ 5 vs 7 $\pm$ 4, p = 0.0001) at the repeat procedure compared to men with a failed repeat attempt. however this difference disappeared after adjusting for variable in logistic regression suggesting FSH and testicular volume had independent impact in predicting the outcome.	None included		Ranjith Ramasamy, Joseph A. Ricci, Robert A. Leung, Peter N. Schlegel . Successful Repeat Microdissection Testicular Sperm Extraction in Men With Nonobstructive Azoospermia . The Journal of Urology .2011,	None studied	As in primary outcome measure	This is retrospective case series of men with NOA. The study results are subject to bias and confounding due to lack of a study design and lack of randomisation and lack of control. However in the absence of any other good quality studies this provides some but low level evidence hence has been included. Results show that Sperm retrieval is higher with repeat attempts, however it is not clear from the study on the number of repeat attempts by study subjects or the characters of the people who underwent repeat by their number of attempts.
2-	Other	628 with azoospermia with 784 procedures	Repeat sperm retrieval	Clinical effectiveness of the intervention	Sperm retrieval rate	Of the 784 procedures performed on the 628 men with NOA, sperm could be retrieved in 384 procedures (49%). During the first testicular sperm extraction (TESE) procedure, sperm could be extracted in 261 men with NOA (41.6%). A total of 103 men had a second attempt, 34 had a third attempt, 11 had a fourth attempt, 6 had a fifth attempt and 2 had a sixth attempt. In these cycles, sperm could be extracted in, respectively, 77 (74.7%), 28 (82.3%), 11 (100%), 5 (83.3%) and 2 (100%) men.	None included		Valérie Vernaevae 1, 3, G. Verheyen 2, A. Goossens 2, A. Van Steirteghem 2, P. Devroey 2 and H. Tournaye 2 . How successful is repeat testicular sperm extraction in patients with azoospermia. Hum. Reprod. . 2006,			This is retrospective case series of men with NOA. The study results are subject to bias and confounding due to lack of randomisation and lack of control. However in the absence of any other good quality studies this provides some but low level evidence hence has been included. Although the study the rate of retrieval improved with repeat attempts there is no information on the characters of patients by the number of attempts, the role of chance confounders due to self-selection and lack of control as an explanation for the results is quite possible.

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2++	Other	143 men	ICSI in patient with Y AZFc chromosome microdeletion	Clinical effectiveness of the intervention	Clinical outcomes of endometrial thickness, transferred embryos, good embryo rates, implantation rates, biochemical pregnancy rates, clinical pregnancy rates, ectopic pregnancy rates, miscarriage rates, preterm birth rates, the ratio of male and female babies, new-born body height, new born weight, low birth weight and birth defects	There were no significant differences between groups in clinical outcomes	None		Xiao-hong Liu, Jie Qiao, Rong Li, Li-ying Yan, Li xue Chen . Y chromosome AZFc microdeletion may not affect the outcomes of ICSI for infertile males with fresh ejaculated sperm. Journal of Assisted Reproduction and Genetics J. 2013,	None	As in primary outcome measure	A retrospective case control study of men with NOA with some good description of study design and reasonable association study factors and outcome. The results show that men with Y chromosome AZFc microdeletion had similar clinical outcomes compared to men with no chromosome Y deletion when treated ICSI for infertility.
2-	Other	1919 azoospermic and oligospermic. Of these 168 men were with AZF deletions	Microsurgical sperm retrieval	Clinical effectiveness of the intervention	Positive surgical sperm retrieval	The success rates for surgical sperm retrieval were 7.1% (1/14) in men with AZFbc deletion and 54.8% (17/31) in the isolated AZFc deletion group. No sperm was obtained from the patients with AZFa or AZFb deletions who underwent microsurgical sperm retrieval. In the isolated AZFc deletion group, there were significant differences between azoospermic and severely oligozoospermic patients in terms of testicular volume and serum levels of follicle-stimulating hormone and luteinizing hormone, whereas no significant differences were found when the group was divided by surgical sperm retrieval outcomes.	None included in the abstract		Se Hwan Park, Hyo Serk Lee, Jin Ho Choe, Joong Shik Lee and Ju Tae Seo . Success Rate of Microsurgical Multiple Testicular Sperm Extraction and Sperm Presence in the Ejaculate in Korean Men With Y Chromosome Microdeletions . Korean J Urol. . 2013,	None		A retrospective case series of outcome of surgical sperm retrieval in men with chromosomal Y deletions. The results show deletions of the AZFa and AZFb regions are associated with severe spermatogenic impairment. However, more than half of men with an AZFc deletion had sperm within the ejaculate or testis for in vitro fertilisation with intracytoplasmic sperm injection.

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2-	Other	149 patients with microdeletions in patients with azoospermia and oligozoospermia	mTESE	Clinical effectiveness of the intervention	Positive surgical sperm retrieval	Of 149 microdeletions in azoospermic and oligozoospermic patients, two-thirds were AZFa, AZFb, AZFb+c, or complete Yq deletions. Virtually all microdeletions in oligozoospermic patients were AZFc deletions. 41 patients with microdeletions underwent microdissection TESE. Microdissection TESE failed in all patients with AZFa, AZFb, AZFb+c, and complete Yq deletions. Sperm were retrieved in 15/21 AZFc deleted patients (71.4%). Clinical pregnancy was achieved in 10/15 azoospermic AZFc deleted patients for whom sperm were successfully retrieved	None included in the abstract		Stahl PJ1, Masson P, Mielnik A, Marean MB, Schlegel PN, Paduch DA.. A decade of experience emphasizes that testing for Y microdeletions is essential in American men with azoospermia and severe oligozoospermia. . Fertil Steril. . 2010 ,			A retrospective case series of the outcome of surgical sperm retrieval in men with chromosomal Y deletions. The results show deletions of the AZFa and AZFb regions are associated with severe spermatogenic impairment and poor success for surgical sperm retrieval. However, 71% of men with an AZFc deletion had a positive sperm retrieval and 66% of these resulted in successful pregnancy
0	Single study	58 patients	mTESE	Clinical effectiveness	Positive sperm retrieval	Spermatozoa were successfully retrieved in 27 men by m-TESE (46.5%). The mean (range) FSH level was 19.4 (1.6–58.5) IU/L. There was no correlation in age (mean age retrieved 38.1 years, not retrieved 39.7 years, P = 0.38), FSH levels (mean FSH retrieved 21.4 IU/L, not retrieved 17.7 IU/L, P = 0.3) and the ability to find sperm by m-TESE. However, there was a significant difference in testosterone levels and sperm retrieval (mean testosterone retrieved 14.99 nmol/L, not retrieved 11.39 nmol/L, P < 0.05). Patients with a diagnosis of Sertoli-cell-only (SCO) syndrome [14/35 (40%)] and maturation arrest [four of 11 (36%)] had lower sperm retrieval rates than those in the hypospermatogenesis group [nine of 12 (75.0%)] (P < 0.05). There were no significant complications after m-TESE.	None	0	Kalsi J.S., Shah P., Thum Y., Muneer A., Ralph D.J. and Minhas S. Salvage microdissection testicular sperm extraction; outcome in men with non-obstructive azoospermia with previous failed sperm retrievals . BJU Int. . 2015 ,	0	As in primary outcome measure	A retrospective case series of 58 men with NOA who had previously unsuccessfully undergone TESE or TESA. Patients with azoospermic factor AZF a or b were excluded. Spermatozoa were successfully retrieved in 27 men by m-TESE (46.5%). There was no correlation in age (mean age retrieved 38.1 years, not retrieved 39.7 years, P = 0.38), FSH levels (mean FSH retrieved 21.4 IU/L, not retrieved 17.7 IU/L, P = 0.3) and the ability to find sperm by m-TESE. However, there was a significant difference in testosterone levels and sperm retrieval (mean testosterone retrieved 14.99 nmol/L, not retrieved 11.39 nmol/L, P < 0.05). Patients with a diagnosis of Sertoli-cell-only (SCO) syndrome [14/35 (40%)] and maturation arrest [four of 11 (36%)] had lower sperm retrieval rates than those in the hypospermatogenesis group [nine of 12 (75.0%)] (P < 0.05). The generalisability is limited by number of factors including retrospective nature of study, authors do not mention if more than 58 men were available for selection or reasons for exclusion if any. Authors have subgroup analysis by age, FSH level, histology and testosterone level but study was not adequately powered to detect this difference. There is no definition of what constituted a successful sperm retrieval (one vs more than viable sperm), and more importantly patient related outcomes including pregnancy rates, and live birth rates.



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3	Single study	46 patients with nonobstructive azoospermia TESE+mTESE; 134 nonobstructive azoospermia with mTESE only	Salvage-TESE followed by mTESE	Clinical effectiveness	Positive sperm extraction	Salvage microdissection TESE was even successful in 9 of 23 patients (39.1%) in whom testicular histology revealed SCOS	None	0	Akira Tsujimura, Yasushi Miyagawa, Tetsuya Takao, Shingo Takada, Minoru Koga, Masami Takeyama, Kiyomi Matsumiya, Hideki Fujioka and Akihiko Okuyama. Salvage Microdissection Testicular Sperm Extraction After Failed Conventional Testicular Sperm Extraction in Patients With Nonobstructive Azoospermia. THE JOURNAL OF UROLOGY. 2006,	None mentioned	As in primary outcome measure	The purpose of this retrospective cohort study was to understand successful sperm retrieval rate in cohort of men with NOA in whom routine TESE and in vitro fertilisation-ICSI failed. Authors conclude that authors such patients can be rescued by microdissection TESE. However, several study limitations make it difficult to generalise the recommendation to use this approach routinely including small sample size to allow adequate statistical analysis and can't rule out selection bias and confounding. It is also reported that all patients underwent prior TESE procedures elsewhere so poor ability of the lab techniques at the original site to find a sperm rather than on the type of retrieval procedure performed cannot be ruled out. Also there is no definition of what constituted success. This is a practical issue, in that finding only a single sperm might deem a procedure successful when in fact this scenario rarely results in a clinical pregnancy. There is report of complications of the procedure as the procedure can give rise to potential loss of testis from microdissection.
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2++	Single study	355 patients, 258 with cTESE and mTESE, 77 with mTESE only	cTESE	Clinical effectiveness	Positive sperm extraction	The SRR was 33.7% (87/258) in the patients who underwent conventional TESE and spermatozoa were found in 44 more patients and the SRR increased to 50.8% (131/258) when the patients underwent microdissection TESE additionally. The SRR was significantly higher in the conventional and microdissection TESE group (P<.001). The SRR was 20.8% (16/77) in the patients who only. The SRR was 50.6% (81/160) in the patients with FSH levels of 1–15 mIU/mL, 37.7% (46/122) in the patients with FSH levels of 16–30 mIU/mL, and 37.7% (20/53) in the patients with FSH levels of R31 mIU/mL. There was no significant difference between the groups (P>.05). The SRR was 20.8% (16/77) in the patients with testis volumes of <5 mL, 40% (42/105) in the patients with testis volumes of 6–15 mL, and 58.2% (89/153) in the patients with testis volumes of >16 mL underwent microdissection TESE. When testis volume increased, SRR increased significantly (P<.001).	Fertilisation rate, clinical pregnancy rates, Live birth rate	The fertilisation rates were 59.2 and 57.85, the clinical PRs were 50.6% (38/75) and 51.7% (59/114), and the live birth rates were 39.1% (27/69) and 37.1% (39/105) for conventional TESE alone and conventional TESE combined with microdissection TESE, respectively. There was no significant difference between the groups (P>.05).	Tahsin Turunc, M.D., Umit Gul, M.D., Bulent Haydardedeoglu, M.D., Nebil Bal, M.D., Baris Kuzgunbay, M.D., Levent Peskircioglu, M.D., and Hakan Ozkardes, M.D.. Conventional testicular sperm extraction combined with the microdissection technique in nonobstructive azoospermic patients: a prospective comparative study. Fertility and Sterility. 2010.	None reported	As in primary outcome measure	This is prospective case series of men with NOA undergoing surgical sperm extraction assessed by surgical technique, (cTESE, cTESE+mTESE, or mTESE only in men with testicular volume <5ml), FSH levels, Testicular volume, histology. The study also presents important patient related factors such as fertilisation rate, pregnancy rate and live birth rate. This is one of the very few prospective study involving relatively large sample. The study show that the mTESE yielded additional sperm extraction rate when combined with cTESE. Histology (hypospermatogenesis) and testicular volume were positive predictor factors. One of the limitation of the study is small sample size which was not powered to detect the difference between groups in the subgroup analysis. Others being lack of clarity on the number of people in the cTESE+mTESE undergoing mTESE-only patients with negative cTESE or all the 258 irrespective of cTESE results.
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2-	Single study	374 (280 MESA and 94 TESE)	MESA -ICSI	Clinical effectiveness of the intervention	Ongoing pregnancy and live birth rate	There were no significant differences between MESA and TESE cases in terms of age of the female partner, number of oocytes retrieved, number of embryos, or number of embryos transferred. More sperm was found using MESA than using TESE (P<0.001). Similarly, frozen sperm accounted for a significantly higher proportion of cycles in the MESA group compared with the TESE group (60 versus 15%, P <0.001). The live birth rate after MESA-ICSI was significantly higher than after TESE-ICSI (39 versus 24%, P = 0.011). The clinical and ongoing pregnancy rates after MESA-ICSI (47 and 39%, respectively) were also significantly higher than after TESE-ICSI (30 and 24%, respectively). The implantation rate per embryo transferred was 22% after MESA-ICSI and 15% after TESE-ICSI (P =0.035). In a univariable logistic analysis female age, whether MESA or TESE was performed, and the number of oocytes, to be significantly associated with live birth. The unadjusted odds ratio for live birth was 2.0 (95% CI 1.16–3.34) for MESA versus TESE. In multivariable analysis, MESA still resulted in a significantly higher live birth rate than did TESE. Adjusted for the available confounders, the odds ratio for live birth rate was 1.82 (95% CI 1.05–3.67) after MESA versus TESE. There was no difference in the results related to whether fresh sperm or frozen sperm were used, or whether the obstruction was caused by CBVAD or vasectomy.	None	0	van Wely, Madelon; Barbey, Natalie; Meissner, Andreas; Repping, Sjoerd; Silber, Sherman J.. Live birth rates after MESA or TESE in men with obstructive azoospermia: is there a difference?. Human Reproduction (Oxford, England). 2015,	None mentioned	As in primary outcome	This is retrospective case series of 374 cases of obstructive azoospermia undergoing MESA-ICSI or TESA ICSI selected over a period of ten years from 2000-2009. The results show that pregnancy rates and live births rates were significantly higher in patients who had sperms extracted through MESA compared to TESE. This difference was still present after adjusting for other confounders suggesting method of sperm extraction was independently associated with outcomes. Apart from the method of sperm extraction, authors found age of women and number of eggs significantly associate with outcomes. Authors conclude that in cases of obstructive azoospermia with normal spermatogenesis, epididymal sperm obtained through MESA may be more effective than testicular sperm (obtained through TESE) even with the utilization of ICSI techniques. The main limitation of the study are this is retrospective case series with lack of randomisation and no uniform patient selection criteria. Secondly all TESE was done in those men in whom MESA was not feasible or when MESA did not result in any sperm due to epididymal blockage. It may be this subgroup of azoospermic men could in theory have a different fertility potential compared with azoospermic men without blockage or in whom MESA is feasible. Third one being number of other confounders including testicular volume, FSH, markers of epididymal function were not included in the regression analysis. Other limitation being authors have reported that there was no impact of male age based on the finding that most of vasectomy patients were older and there was difference in outcomes patients with vasectomy compared to congenital absence of vas deferens. For the above limitations, the generalisability of study results are limited.
3	Single study	51	PESA-ICSI/IVF	Clinical effectiveness of the intervention	Fertilization rate and pregnancy rate	Viable sperms were identified in 100% of men, but fresh spermatozoa were obtained in 40 patients (78.4%) simultaneously with female egg retrieval. The average fertilization rate in these 40 patients was 77.7% with five embryos not surviving to transfer (12.5%). Pregnancies were confirmed in 48.6% (17/35). Twin gestations occurred in 11.8% (2/17) of cases. Frozen-thawed spermatozoa were used in 11 patients (21.6%). In this subgroup, the average fertilization rate was 73.6% with pregnancies confirmed in 54.5% (6/11). No multiple gestations were generated, and no complications occurred.	None reported	0	Kovac, Jason R.; Lehmann, Kyle J.; Fischer, Marc Anthony. A single-center study examining the outcomes of percutaneous epididymal sperm aspiration in the treatment of obstructive azoospermia. Urology Annals. 2014,	Authors report that no complications were noted	As in primary outcome measure	This is a retrospective case series of 51 men with OA who underwent PESA for sperm extraction for fertilization. There are no comparators. The results of the study show that of the 40 patients who had successful sperm extraction along with egg retrieval from their female partners 77.7% had successful fertilization with 5 failures. Pregnancy rate was 48.6% but no reporting on live birth rates. There was no difference between fresh vs frozen groups in fertilization rates or pregnancy rates. The generalisability of this study are limited by retrospective nature of study, with lack of patient selection criteria. Also as the results are not adjusted for confounders including age, FHS, etiology of obstruction, female age groups.

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3	Other	Not mentioned	MESA	Clinical effectiveness of the intervention	Sperm retrieval rate and yield rate	<p>MESA - Done under general or regional anaesthesia with a sperm retrieval rate of 95%–100% of cases. Yield- 15–95* 106 total sperm with 15%–42% total motility, cryopreservation possible in 98%–100% of cases with an average of 5.3–7.6 vials per patient.</p> <p>PESA - Done under local anaesthesia with a sperm retrieval rate of 80%–100%. Yield- Thousands to millions of sperm with variable motility (poorly reported in most studies), cryopreservation possible in 43%–96% of cases.</p> <p>Testicular fine needle aspiration: Done under local anaesthesia with a sperm retrieval rate of 52%–100%. Yield-Hundreds of thousands to millions of sperm with variable motility (poorly reported in most studies), cryopreservation possible in 38% of cases in one study.</p> <p>Testicular large needle aspiration - Done under local anaesthesia with a sperm retrieval rate of 98%–100%. Hundreds of thousands to millions of sperm with variable motility (poorly reported in most studies), cryopreservation possible in 100% of cases in one study.</p> <p>Testicular core needle biopsy – Done under local anaesthesia with a sperm retrieval of 82%–100%. Yield-Hundreds of thousands to millions of sperm with variable motility (poorly reported in most studies), often sufficient for cryopreservation (poorly reported).</p> <p>TESE- Done under local or general anaesthesia with a sperm retrieval rate of 100%. Yields-Hundreds of thousands to millions of sperm in most cases (poorly reported in most studies), usually sufficient for cryopreservation (poorly reported).</p> <p>Microdissection TESE-Done under local or general anaesthesia with sperm retrieval rate of 100%. Hundreds of thousands to millions of sperm in most cases (poorly reported in most studies), usually sufficient for cryopreservation (poorly reported).</p>	None reported	0	Bernie, Aaron M.; Ramasamy, Ranjith; Stember, Doron S.; Stahl, Peter J.. Microsurgical epididymal sperm aspiration: indications, techniques and outcomes. Asian Journal of Andrology. 2013.	None reported in as rates by different procedure. Authors mention about complications of MESA	As in primary outcome	This is a narrative review of MESA in OA including patient selection, lab investigation surgical techniques. It also includes comparison of MESA against other methods of for sperm retrieval and yield. The paper does not include any search methods, patient selection criteria or any statistical methods for polling the data. Therefore the generalisability of studies in poor.
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3	Single study	255	PESA	Clinical effectiveness of the intervention	Sperm motility as assessed by embryologist in consultation with urologist	<p>Motile sperm were detected in 192 patients (75.3%), rare motile sperm in 24 (9.4%), non-motile sperm in 27 (10.6%), and no sperm in 12 (4.7%). Age was significantly related to presence of motile sperm. There was a significantly higher median age (P = .0234) in men who had no sperm (45 years) or non-motile sperm (46 years) compared with those who had motile (41 years) or rare motile sperm (40 years).</p> <p>There was no difference among the groups in terms of median testicular volume or diagnosis groups. However on multivariate analysis, larger testicular volume was independently prognostic for improved motile sperm retrieval rates (P = .0056) whereas increased paternal age strongly trended toward lower rates (P = .0589).</p>	None reported	0	Yafi, Faysal A.; Zini, Armand. Percutaneous epididymal sperm aspiration for men with obstructive azoospermia: predictors of successful sperm retrieval. Urology. 2013,	None reported	As in primary outcome	<p>A retrospective case series with large sample size of 255 men with azoospermia undergoing PESA for sperm extraction. The primary outcome was sperm motility and the results show that age of patients and testicular volume were independently associated with sperm motility. Larger testicular volume was independently prognostic for improved motile sperm retrieval rates (P =.0056) whereas increased paternal age strongly trended toward lower rates (P =.0589).</p> <p>The results of the study is limited because of retrospective nature of the study and lack of information on other important outcomes including fertilization, pregnancy rates and live birth rate.</p>
3	Single study	88 patients with 93 MESA procedures	Microsurgical epididymal sperm aspiration (MESA)	Clinical effectiveness of the intervention	Sperm concentration, global motility in sperm aspirate, clinical pregnancies, births	<p>Mean sperm concentration was <math>40.9 \times 10^6</math> sperms/ml. Global and progressive motility were 24.8 and 7.5% respectively. 33/88 (37.5%) did not contain progressive motile spermatozoa (WHO class a). In 33 ICSI cycles with frozen-thawed epididymal spermatozoa pregnancy rate was 42.4%.</p> <p>There was no significant difference in two subgroup (CBAVD and failed microsurgical reconstruction) for primary outcomes including sperm concentration, global motility.</p>	None mentioned	0	Schroeder-Printzen, I.; Zumbé, J.; Bispink, L.; Palm, S.; Schneider, U.; Engelmann, U.; Weidner, W.. Microsurgical epididymal sperm aspiration: aspirate analysis and straws available after cryopreservation in patients with non-reconstructable obstructive azoospermia. MESA/TESE Group Giessen. Human Reproduction (Oxford, England). 2000.	None included	As in primary outcome	<p>This is a retrospective case series of MESA for 88 men with obstructive azoospermia mainly due to CBAVD and failed microsurgical reconstruction). The results show that mean sperm concentration was <math>40.9 \times 10^6</math> sperms/ml. Global and progressive motility were 24.8 and 7.5% respectively. 33/88 (37.5%) did not contain progressive motile spermatozoa (WHO class S). In 33 ICSI cycles with frozen -thawed epididymal spermatozoa pregnancy rate was 42.4%.</p> <p>There was no significant difference in two subgroup (CBAVD and failed microsurgical reconstruction) for primary outcomes including sperm concentration, global motility.</p> <p>The generalisability study are limited to retrospective case selection, lack of adjustment for confounders including age, testicular volume, and other endocrinology markers. Another factor is the experience of surgeons and its relation to outcome. It is not clear if there were more than one surgeon involved.</p>

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3	Other	100	PESA, MESA, TESE	Clinical effectiveness of the intervention	Viable sperm	<p>PESA was performed in all 109 retrieval cycles with a successful sperm retrieval rate of 61%. When PESA failed to retrieve a sufficient number of viable sperm, MESA was subsequently performed with a sperm retrieval rate of 93%. Three cases, which had failed retrieval with both the PESA and MESA procedures, received TESE successfully.</p> <p>The rates of fertilization and pregnancy were 56% and 39% in the 66 PESA-ICSI cycles, respectively, and 47% and 45% in the 40 MESA-ICSI cycles. No significant differences were found in fertilization rates or pregnancy rates among the various sperm retrieval methods and obstruction etiologies. The overall mean fertilization rate and pregnancy rate were 51% and 41%, respectively.</p>	None mentioned in the abstract	0	<p>Lin, Y. M.; Hsu, C. C.; Kuo, T. C.; Lin, J. S.; Wang, S. T.; Huang, K. E..</p> <p>Percutaneous epididymal sperm aspiration versus microsurgical epididymal sperm aspiration for irreparable obstructive azoospermia--experience with 100 cases.</p> <p>Journal of the Formosan Medical Association = Taiwan Yi Zhi. 2000,</p>	None mentioned in the abstract	0	<p>No full text was available for this study. Based on the abstract it appears that rate of sperm retrieval was 100% for all the three methods when tried sequentially in the order of PESA, MESA, and TESE. The overall fertilization rate pregnancy rate were 51% and 41% respectively. Main limitation of the study are retrospective case selection, lack of definition of successful sperm retrieval, lack of details of causes of obstructive azoospermia. Also the results are not adjusted for confounding factors including age, testicular volume, hormonal factors and also experience of surgeons.</p>
3	Single study	24 couples with 39 ICSI procedures	MESA, PESA and TESE in those who failed PESA	Clinical effectiveness of the intervention	Sperm retrieval, fertilisation, embryo transfer, pregnancy, rate and live birth	<p>MESA was performed in the first four patients only, and was successful in all. Subsequently, PESA was introduced as the first approach for epididymal sperm retrieval for future cases. PESA was successful in 18/29 (62%) procedures. In 11 cases of failed epididymal sperm retrieval an excisional testicular biopsy was performed and viable spermatozoa were found in 9/11 (82%) biopsies.</p> <p>Successful embryo transfer was performed in 92% (36/39) of procedures and resulted in a clinical pregnancy in 13/39 procedures. Ongoing pregnancy was achieved in 10/39 procedures. One pregnancy was terminated due cytogenetic abnormality (47,XXF18, Edwards) syndrome) and other nine pregnancies resulted in the live birth of 10 children, without any congenital abnormalities.</p>	None reported	0	<p>Dohle, G. R.; Ramos, L.; Pieters, M. H.; Braat, D. D.; Weber, R. F..</p> <p>Surgical sperm retrieval and intracytoplasmic sperm injection as treatment of obstructive azoospermia.</p> <p>Human Reproduction (Oxford, England). 1998,</p>	None included in the paper	As in primary outcome	<p>This is a retrospective case series of 24 men with azoospermia undergoing MESA, PESA or TESE following a failed PESA. The reporting of outcomes was inconsistent in that for MESA are reported by patients where as for other two interventions PESA and TESE outcomes are reported by total number of ICSI cycles. Only 4 patients underwent MESA and there was 100% successful sperm retrieval. 62% undergoing PESA had successful sperm retrieval and of the 11 who were unsuccessful on PESA underwent TESE and 9 had successful spermatozoa extraction. In 92% of ICSI cycled led to successful embryo transfers, 33% pregnancies and 25% to live births. The results are limited due to retrospective nature patient selection, lack of controlling for confounders in the analysis and lack of consistency in reporting outcomes.</p>

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3	Single study	9	MESA	Clinical effectiveness of the intervention	During a planned MESA , TFNA and Percbiopsy were obtained from the same testis.	Spermatozoa was obtained in all patients with MESA and TFNA and 6/9 (67%) using Percbiopsy. The mean number of spermatozoa was highest using MESA and was significant higher compared to other two methods. Average sperm motility was higher for MESA, (15%) compared to Percbiopsy (25) and TFNA (0%).	None included	0	Sheynkin, Y. R.; Ye, Z.; Menendez, S.; Liotta, D.; Veeck, L. L.; Schlegel, P.. Controlled comparison of percutaneous and microsurgical sperm retrieval in men with obstructive azoospermia. Human Reproduction (Oxford, England). 1998,	3 patients (33%) developed haematocele after percutaneous aspiration and biopsy.	0	This is a retrospective case series of 9 men comparing MESA, TFNa and percbiopsy obtained from same testis and at same time. The results show spermatozoa were retrieved in all 9 patients using MESA and TFNA and on 67% patients using Percbiopsy. MESA resulted in retrieving higher mean number of spermatozoa compared to other two methods and had higher proportion of motile sperms compared to other methods. The generalisability of study are limited due to its retrospective case selection, small number of patients, and lack of adjustment for potential confounders.
2+	Systematic review	0	MESA, PESA, TESE and TESA	Clinical effectiveness of the intervention	Sperm retrieval rate, embryo transfer rate, fertilisation rate, prgenancy rate	Nice Review conclusions: Obstructive azoospermia- based on a systematic review (Cochrane review) -MESA compared to epididymal micropuncture achieved lower pregnancy (OR 0.19, 95% CI 0.04 to 0.83) and fertilisation rates (OR 0.16, 95% CI 0.05 to 0.48). [Evidence level 1a] All the surgical methods used in obstructive azoospermia are successful in sperm recovery. NICE review reported very low failure rates for different types of surgical methods MESA 1.7% of men (1/59) to 22% of men (2/9) PESA- 5% in men with failed reversed vasectomy, 11% in men with CBAVD and 15.8% to 17% of initiated cycles, TESA -0%. NICE review suggests that permatozoa can be retrieved from the testis in couples in whom epididymal aspiration failed. When spermatozoa cannot be recovered by one technique another one can be employed, for example, TESE after MESA. Spermatozoa obtained from testicular can be successful in achieving fertilisation and pregnancies for couples in whom epididymal aspiration failed. Nonobstructive azoospermia:	None reported separately	0	National Collaborating Centre for Women's and Children's Health . Fertility: assessment and treatment for people with fertility problems.. Fertility: assessment and treatment for people with fertility problems.. 2013.	Not reported	As in primary outcome	NICE evidence is presented with a good quality methodology including search methods, patient selection criteria and statistical methods for pooling the data and analysis. However the evidence included for the review is based on retrospective case series with poor reporting and patient selection criteria and are of level 3 evidence. In summary although the review has robust methodology because of the low level of evidence studies included in evaluating the various surgical sperm retrieval methods the results of the study are not generalisable.





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### Appendix

#### Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Male patients Humans Infertile couples Azoospermia or severe oligozoospermia confirmed on two semen analyses 3 months apart
Updated search terms - Population	azoospermia OR low sperm count OR male factor infertility OR male infertility OR male subfertility OR oligozoospermia OR klinefelters OR klinefelters syndrome OR klinefelter's syndrome OR varicocele
Updated search terms - Intervention	epididymal sperm aspiration OR epididymal sperm retrieval OR microsurgical sperm extraction OR microsurgical testicular exploration OR microsurgical testicular exploration sperm extraction OR percutaneous epididymal sperm aspiration OR sperm aspiration OR sperm extraction OR surgical sperm removal OR surgical sperm retrieval OR testicular aspiration OR testicular exploration OR testicular exploration and sperm extraction OR testicular exploration sperm extraction OR testicular sperm aspiration OR

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	<p>testicular sperm retrieval OR          ICSI OR          Intracytoplasmic sperm injection OR          micro TESE OR          MESA OR          micro testicular exploration OR          predictive factors OR          repeat sperm extraction OR          sperm harvesting OR          sperm retrieval OR          surgical sperm extraction OR          varicocele</p>
<p>Updated search terms -          Comparator</p>	<p>assisted reproduction technique OR          assisted reproduction techniques OR          conventional treatment OR          donor sperm OR          fertility treatment</p>
<p>Updated search terms -          Outcome</p>	<p>live birth rate OR          live birth rates OR          pregnancy OR          psychological impact OR          quality of life OR          success rate OR          success rates</p>

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<b>Inclusion criteria</b>	<b>General inclusion criteria</b>
	<p>In order of decreasing priority, the following are included:</p> <ol style="list-style-type: none"> <li>1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant ( e.g. no further updated systematic review available)</li> <li>2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial / the RCT is one of the few or only high quality clinical trials available) <ul style="list-style-type: none"> <li>&gt;&gt;&gt;&gt; If studies included reach 30, inclusion stops here</li> </ul> </li> <li>3. All relevant case control and cohort studies, that qualify after exclusion criteria <ul style="list-style-type: none"> <li>&gt;&gt;&gt;&gt; If studies included reach 30, inclusion stops here</li> </ul> </li> <li>4. All relevant non analytical studies ( case series/ reports etc) that qualify after exclusion criteria <ul style="list-style-type: none"> <li>&gt;&gt;&gt;&gt; If studies included reach 30, inclusion stops here</li> </ul> </li> <li>5. Expert opinion</li> </ol>
<b>Exclusion criteria</b>	<b>Specific inclusion criteria</b>
	<p>Search: Population AND Intervention</p> <p>Filter: English; 10 years;</p>
<b>Exclusion criteria</b>	<b>General exclusion criteria</b>
	<p>Studies with the following characteristics will be excluded:</p> <ol style="list-style-type: none"> <li>1. Do not answer a PICO research question</li> <li>2. Comparator differs from the PICO</li> <li>3. &lt; 50 subjects (except where there are fewer than 10 studies overall)</li> <li>4. No relevant outcomes</li> <li>5. Incorrect study type</li> <li>6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site</li> </ol>
<b>Exclusion criteria</b>	<b>Specific exclusion criteria</b>
	None