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Effectiveness and safety of microsurgical testicular sperm extraction in infertile men with non-obstructive azoospermia

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Effectiveness and safety of microsurgical testicular sperm extraction in infertile men with non-obstructive azoospermia

[Effektivitet och säkerhet av mikrokirurgisk testikelspermaextraktion hos infertila män med icke-obstruktiv azoospermi]

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1. Abstract

Background
Azoospermia, absence of sperm in the ejaculate, affects approximately 1% of the male population. About 40 men with infertility are referred to the Reproductive medicine department at Sahlgrenska University Hospital in Gothenburg annually. Testicular Sperm Aspiration (TESA, needle punction) or Percutaneous Epididymal Sperm Aspiration (PESA) are used to find spermatozoa and categorises azoospermia patients into obstructive or non-obstructive azoospermia (NOA). TESA is a blind method and failure to retrieve spermatozoa is common. With testicular sperm extraction (TESE), multiple blind surgical biopsies are taken from the testicles. TESA and TESE results are comparable concerning sperm retrieval rate, clinical pregnancy rate and live birth rate. TESA is the currently used technique in our hospital. A recent technique, micro-TESE, allows a more extensive search for spermatozoa. Under an operation microscope, the tunica albuginea is widely opened and small testicular tissue samples are excised and immediately examined for spermatozoa under a microscope. If needed, further samples are taken from the ipsi- and contralateral testicles.

Questions at issue
Is micro-surgical TESE, compared with TESA, in men with non-obstructive azoospermia safe and effective regarding sperm retrieval, clinical pregnancy and live birth rates? Is micro-TESE sufficiently effective and safe after a failed TESA?

Methods
Two authors performed searches (03/2019) in PubMed, Embase and the Cochrane Library, selected studies, independently assessed the abstracts and made a first selection of full-text articles. These were sent to all authors and inclusion was finally decided in consensus. Data were extracted, and cohort studies were critically appraised. When possible, data were pooled in meta-analysis and presented as forest plots.

Results
One cohort study and 19 case series were identified. The cohort study included 100 patients and compared micro-TESE on one testicle with TESA on the other testicle in the same individual.
Sperm retrieval rate was reported in 16 studies with 7917 men and was 52% for micro-TESE and 10% for TESA in the cohort study. The pooled sperm retrieval rate of the case series, showing great heterogeneity, was 45% (95% CI 39 to 51%).
Conclusion: In patients with NOA, micro-TESE compared with TESA may result in significantly higher sperm retrieval rate (GRADE ⊕⊕◯◯).
Clinical pregnancy was reported in six case series including 3892 men. Calculated per micro-TESE procedure, the pooled clinical pregnancy rate was 20% (95% CI 15 to 25%). Clinical pregnancy rate per successful micro-TESE (i.e. resulting in sperm retrieval) ranged from 36 to 50% (95% CI).
Live birth was reported in five case series including 3252 men. Calculated per micro-TESE procedure, the pooled live birth rate was 15% (95% CI 9 to 20%). Live birth rate per successful micro-TESE ranged from nine per cent to 20% (95% CI).
Complications were reported in eight studies including 1563 men. In the cohort study, ultrasound follow-up at one, three and six months detected early changes (10% vs 22% for Micro-TESE vs TESA) but all were resolved within two months. Seven case series reported complications (range 0-9%), mainly minor, not requiring reoperations.
Conclusion: In patients with NOA it is uncertain whether there is any difference in complication rates for micro-TESE compared with TESA (GRADE ⊕◯◯◯).
No study was found, evaluating micro-TESE after previously failed TESA.

Concluding remarks
One cohort study comparing micro-TESE with TESA and 19 case series were identified. Sperm retrieval rate may be higher with micro-TESE compared with TESA (GRADE ⊕⊕◯◯) and the pooled sperm retrieval rate of the case series was 45% (95% CI 39% to 51%). Clinical pregnancy and live birth rates (95% CI) of micro-TESE were 15 to 25% and 9 to 20% respectively. Complications, mainly minor, ranged 0-9%. In summary, micro-TESE may improve sperm retrieval in men with NOA and is associated with few severe complications. There is a need of large high quality studies comparing results of micro-TESE with TESA.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Azoospermi, frånvaro av spermier i ejakulatet, föreligger hos ungefär en procent av män. Omkring 40 infertila män remitteras årligen till Reproduktionsmedicin vid Sahlgrenska Universitetssjukhuset i Göteborg. Perkutan spermieaspiration via nålpunktion av testiklar (TESA) eller bitestiklar (PESA) används för att hitta spermier och kategorisera azoospermi som obstruktiv eller icke-obstruktiv (NOA). TESA är en blind metod och det är vanligt att man inte hittar spermier. Vid testikulär spermieextraktion (TESE) tas flera kirurgiska biopsier blint från testiklarna. TESA och TESE har likvärdiga resultat och TESA är den nu använda metoden på vårt sjukhus. En nyare metod, mikro-TESE, möjliggör mer omfattande sökning efter spermier. I operationsmikroskop öppnas bindvävskapseln kring testiklarna och små kirurgiska testikelvävnadsprov undersöks omedelbart för spermier i mikroskop med × 200 förstoring. Om nödvändigt tas fler prov från samma eller den andra testikeln för att hitta spermier.

Frågeställning
Är mikro-TESE, jämfört med TESA, hos män med NOA en säker och effektiv metod att hitta spermier att använda vid provrörsbefruktning för att nå graviditet och födsel? Är mikro-TESE en tillräckligt effektiv och säker metod att hitta spermier hos män där TESA misslyckats?

Metod
Litteratursökning utfördes (03/2019) i PubMed, Embase och Cochrane Library av två författare som selekterade studier, oberoende granskade abstracts och gjorde ett första urval av fulltextartiklar. Dessa skickades till alla författare och slutlig inklusion beslutades vid ett konsensusmöte. Data extraherades och jämförande studier granskades kritiskt. När data var lämpliga för meta-analys utfördes detta.

Resultat
En kohortstudie och 19 fallserier identifierades. Kohortstudien inkluderade 100 patienter och jämförde Mikro-TESE på ena med TESA på andra testikeln hos samma individ.
Utbyte av spermier rapporterades i 17 studier inkluderande 7917 män och var 52% och 10% för mikro-TESE respektive TESA i kohortstudien. Den sammanvägda frekvensen för utbyte av spermier i 16 fallserier, vilka uppvisade stor heterogenitet, var 45% (95% KI 39-51%).
Slutsats: Vid NOA kan Mikro-TESE jämfört med TESA resultera i signifikant högre frekvens av utbyte av spermier (GRADE ⊕⊕◯◯).
Klinisk graviditet rapporterades i sex fallserier inkluderande 3892 män och frekvensen var 20% (95% CI 15-25%) per utförd mikro-TESE och varierade från 36 till 50% (95% KI) per framgångsrik mikro-TESE.
Levande fött barn rapporterades i fem fallserier inkluderande 3252 män och frekvensen var 15% (95% KI 9-20%) per utförd mikro-TESE och varierade från 9% till 20% (95% KI) beräknat per framgångsrik mikro-TESE.

Komplikationer rapporterades i åtta studier inkluderande 1563 män. I kohortstudien identifierade ultraljud vid en, tre och sex månader tidiga förändringar (10% vs 22% för mikro-TESE vs TESA) vilka alla försvann inom två månader. Sju fallserier rapporterade komplikationsfrekvenser mellan noll och nio procent, nästan uteslutande mindre allvarliga komplikationer.
Slutsats: Hos patienter med NOA är det osäkert om komplikationsfrekvensen för mikro-TESE är lägre än för TESA (GRADE ⊕◯◯◯).
Ingen studie hade rapporterat resultat av micro-TESE hos män som tidigare genomgått TESA utan att finna spermier.

Sammanfattande slutsats
En kohortstudie som jämförde Mikro-TESE med TESA och 19 fallserier identifierades. Frekvensen utbyte av spermier kan vara högre med mikro-TESE jämfört med TESA (GRADE ⊕⊕◯◯) och den sammanvägda frekvensen för utbyte av spermier var 45% (95% KI 39-51%). Frekvenserna (95% KI) av klinisk graviditet och levande fött barn per utförd mikro-TESE var 15-25% respektive 9-20%. Komplikationer, nästan uteslutande mindre allvarliga, varierade mellan noll och nio procent i fallserierna. Sammanfattningsvis kan mikro-TESE öka frekvensen av utbyte av spermier hos män med NOA med få rapporterade allvarliga komplikationer. Det finns ett behov av stora högkvalitativa studier jämförande resultaten av mikro-TESE med TESA.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, June 12 2019

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings (Micro-TESE vs TESA)

Outcomes /mTESE procedure	**Study design Number of studies**	**Relative effect (95% CI)**	**Absolute effect**	**Certainty of evidence GRADE[1]**
Sperm retrieval	1 cohort	RR 5.2 (2.8 to 9.6) p<0.001	52% vs 10%	Low ⊕⊕◯◯[2]
Clinical pregnancy	0 controlled studies 5 case series	-	Estimated rate 20% (95% CI 15-25)	-
Live birth	0 controlled studies 4 case series	-	Estimated rate 15% (95% CI 9-20)	-
Complications	1 cohort	RR 0.46 (0.23 to 0.91) p=0.034	10% vs 22%	Very low ⊕◯◯◯[3]

[1]Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[2]Downgraded one level due to some study limitations, remarks on directness and since judgement on consistency not possible (only one study). Upgraded one level due to large effect.

[3]Downgraded one level due to some study limitations and imprecision.

4. Abbreviations/Acronyms

IVF: In Vitro Fertilisation
ICSI: Intra Cytoplasmic Sperm Injection
KS: Klinefelter syndrome
Micro-TESE: Microsurgical Testicular Sperm Extraction
NOA: Non-Obstructive Azoospermia
OA: Obstructive Azoospermia
PESA: Percutaneous Epididymal Sperm Aspiration
RCT: Randomised Controlled Trial
SRR: Sperm Retrieval Rate
TESA: Testicular Sperm Aspiration
TESE: Testicular Sperm Extraction (conventional open surgical without microscope)

5. Background

Infertility

Infertility is common and associated with important psychological, economical, demographical and medical implications. It involves a couple, rather than a single individual. Infertility is classified as a disease, defined by the failure to achieve a pregnancy after 12 months or more of appropriate, timed and unprotected intercourse (Mascarenhas et al., 2012, Zegers-Hochschild et al., 2009). The prevalence of infertility has been reported to be about 15% in females between 15 and 44 years of age, but an unbiased prevalence of male infertility in the general population has not been possible to estimate (Thoma et al., 2013, Barratt et al., 2017). Causes of infertility are divided into three major groups: female, male and mixed factors. Male factor is responsible for about 30% of all cases. The aetiologies for this form of infertility include endocrine and systemic disorders, primary testicular defects in spermatogenesis, sperm transport disorders and idiopathic male infertility (de Kretser, 1997, Jungwirth et al., 2012).

The concentration of spermatozoa in a man's ejaculate is considered normal when it is >15 million spermatozoa/ml, according to the World Health Organization (Cooper et al., 2010). Men with infertility usually have lower concentration of spermatozoa in their ejaculate and sometimes just a few or no spermatozoa at all. Since the 1990s methods for in vitro fertilisations (IVF) have developed rapidly. Fertilisation is performed either by standard IVF, where oocytes are inseminated (mixed) with spermatozoa or by intracytoplasmic sperm injection (ICSI) (Palermo et al., 1992). ICSI is a technique in which a single spermatozoon is injected directly into the cytoplasm of a mature oocyte. The results, concerning fertilization, livebirth and children outcome are comparable between standard IVF and ICSI. Around 50% or more of all IVF cycles are today performed by ICSI (de Geyter et al., 2018). Retrieval of spermatozoa by needle aspiration from the testicles or epididymis or by surgical biopsies from the testicles in combination with ICSI, has been shown to be an effective treatment for men with absence of spermatozoa in the ejaculate, azoospermia (Silber et al., 1995a).

Disease/disorder of interest and its degree of severity

Azoospermia, defined as the absence of sperms in the ejaculate may occur because of reproductive tract obstruction (obstructive azoospermia or OA) or inadequate production of spermatozoa (non-obstructive azoospermia or NOA) (de Kretser, 1997). Azoospermia is one of the known causes of male infertility in couples seeking help for their fertility and family planning.

Prevalence and incidence

Idiopathic azoospermia affects approximately 1% of the male population and 10-15% of males with infertility (Jarow et al., 1989). About 40 patients with the diagnosis of azoospermia are referred annually to the department of Reproductive medicine at Sahlgrenska University Hospital, Gothenburg for further clinical examination and treatment.

Present treatment

The current diagnostic methods used for further investigation of azoospermia are Testicular Sperm Aspiration (TESA) and Percutaneous Epididymal Sperm Aspiration (PESA) (Silber et al. 1995b). Use of these methods enables the physician to categorise patients into the OA or NOA groups. TESA and PESA are day care procedures carried out with local anaesthesia and requiring about 30 minutes. The TESA method is a blind method, in which many needle biopsies are taken by puncturing different areas of the testicles to find testicular tubules containing spermatozoa. If there are small or very small areas of focal spermatogenesis in the testicle tissue there would, using the TESA method, be a great risk that these blind biopsies do not grasp the target areas. Another method used to find sperms in men with NOA, is (conventional) testicular sperm extraction (TESE) in which multiple blind surgical biopsies are taken from the testicles. If spermatozoa are found by either of these methods, they could be used to fertilise oocytes using ICSI. A successful procedure gives the man a chance to become a biological father.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

The patients referred for further diagnostic investigations regarding azoospermia will be subjected to the PESA/TESA procedure after the preliminary clinical examination and hormonal and chromosomal tests. The average wait time for PESA/TESA is about three months.

Number of patients per year who undergo current treatment regimen

About 35 patients per year undergo PESA/TESA procedures at the Sahlgrenska University Hospital.

Present recommendations from medical societies or health authorities

There are no current recommendations.

6. Health Technology at issue: Microsurgical testicular sperm extraction (Micro-TESE)

This technique allows an extensive search of multiple areas of the testicles rather than a limited biopsy sample that may reflect little of the total testicular function. Briefly, a midline scrotal incision is made and the testicle with the spermatic cord is delivered, preferentially from the side with the larger testicle. The tunica vaginalis is opened and the tunica albuginea visualised. Under an operation microscope the tunica albuginea is widely opened in an equatorial plane around approximately 270 degrees of the testicular circumference with preservation of subtunical blood vessels. After the tunica albuginea is opened the testicular parenchyma is directly examined at ×15 magnification under the operation microscope. Examination includes as much of the testicular parenchyma as necessary until spermatozoa are found. Tissue samples (1 to 15 mg) are excised by tearing out larger, more opaque tubules from surrounding Leydig cell nodules or hyperplasia in the testicular parenchyma. Excised samples are immediately examined for the presence of spermatozoa by mechanically disrupting the testicular tissue and placing a small droplet of dispersed tissue suspension on a glass slide under a phase contrast microscope at ×200 magnification according to the Schlegel method (Schlegel, 1999). Each sample is examined by an experienced embryologist, in our hospital from the in vitro fertilisation team. If no spermatozoa are identified in the initial sample, further samples are taken from the same and, if needed, from the contralateral testicle. Dissection is done through all regions of testicular tissue if needed, preserving the centrifugal pattern of the testicular blood supply. The procedure is terminated when spermatozoa is documented in testicular tissue, all regions of both testicles have been examined with excision of the best appearing tubules, or when further dissection is considered likely to jeopardise the testicular blood supply.

This method gives men with NOA who have had an unsuccessful previous TESA another chance to find testicular spermatozoa. It may enable them to go through an infertility treatment with IVF with their own gametes. In Sweden, micro-TESE is a relatively new method for extraction of spermatozoa. It has been reported to have a higher chance of success and lower risk for complications compared to previously used techniques such as TESA and TESE.

7. Objective

Is micro-surgical TESE, compared with TESA, in men with non-obstructive azoospermia safe and effective regarding sperm retrieval, clinical pregnancy and live birth rates? Is micro-TESE sufficiently effective and safe after a failed TESA?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

PICO 1

P	Men with non-obstructive azoospermia with absence of sperm after a previous TESA
I	Micro-TESE
C	No intervention (excluded donated sperm)
O	Sperm yield (yes/no) Clinical pregnancy Live birth Complications

PICO 2

P	Men with non-obstructive azoospermia without a previous TESA attempt
I	Micro-TESE
C	TESA
O	Sperm yield (yes/no) Clinical pregnancy Live birth Complications

8. Methods

Systematic literature search (appendix 1)

During March 2019 two authors (ME, TS) performed systematic searches in PubMed, Embase and the Cochrane Library. The websites of SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services), Folkehelseinstituttet (Norwegian Institute of Public Health) and NICE were also searched. Reference lists of relevant articles were scrutinised for additional references. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The selected articles were sent to all authors. All authors read the articles independently of one another and decided in a consensus meeting which articles should be included in the assessment. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The included cohort study has been critically appraised using a modified checklist for assessment of cohort studies from SBU. The results of each article have been summarised per outcome in Appendix 4.

Data were extracted by at least two authors per outcome. When possible, data were pooled in meta-analyses and presented as forest plots. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 8). The certainty of evidence was graded according to the GRADE system (Guyatt, Oxman et al. 2008).

Ongoing research

A search in Clinicaltrials.gov (May 14, 2019) using the search terms *((testicular sperm extraction OR TESE OR sperm retrieval OR testicular extraction of spermatozoa OR sperm extraction) AND (micro-dissection OR microdissection OR micro-surgical OR microsurgical)) OR testicular tissue microdissection OR testicular tissue micro-dissection OR micro-TESE OR microTESE OR mTESE OR m-TESE OR MDTESE OR MD-TESE* identified 13 trials.

9. Results

Search results and study selection (Appendix 1)

Literature search (Appendix 1)

The literature search identified 473 articles after removal of duplicates. After reading the abstracts 384 articles were excluded. Another 22 articles were excluded by two authors after reading the articles in full text. The remaining 67 articles were sent to all authors, and 20 articles were finally included in the assessment (Appendix 2). We chose case series with 300 or more cases for evaluating the sperm retrieval, clinical pregnancy and live birth rates by micro-TESE. To evaluate complications, also studies with numbers of cases between 100 and 299 were used. In total 20 studies were included in this review. Only one of these studies was a controlled cohort study and the other were case series.

Results per outcome

PICO 1. Micro-TESE compared with no intervention in patients with NOA with absence of sperm after a previous TESA.

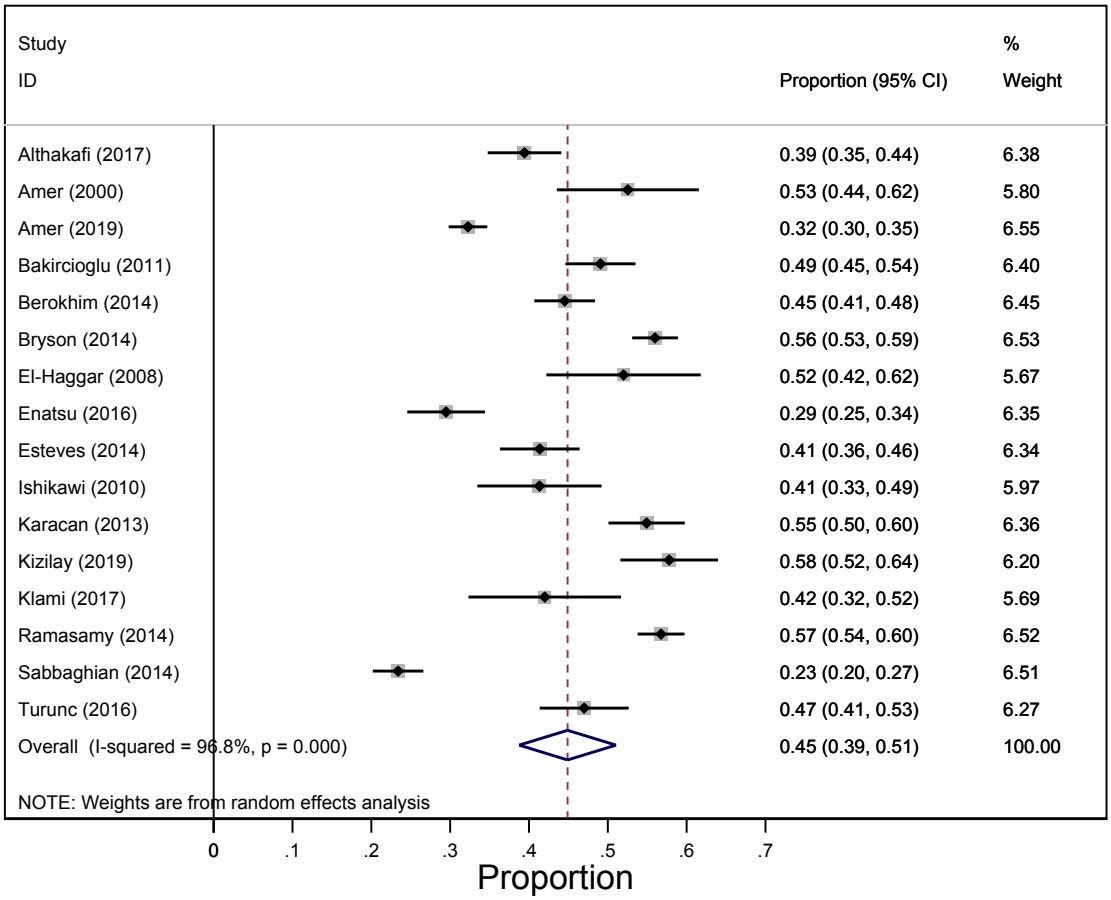
No studies were found.

PICO 2. Micro-TESE compared with TESA in patients with NOA without a previous TESA attempt.

Sperm retrieval (Appendix 4.1)

Sperm retrieval was reported in 16 studies including 7917 patients with NOA. The cohort study, comparing the two techniques on the ipsi- versus the contralateral testicle in 100 patients, showed a sperm retrieval rate of 52% after micro-TESE compared with 10% after TESA (RR 5.2 (95% CI 2.8 to 9.6), $p < 0.001$).

Fig. 1. Meta-analysis of sperm retrieval rate per micro-TESE procedure.



The 15 case series and the micro-TESE procedure from the cohort study were pooled in a meta-analysis showing great heterogeneity, resulting in a pooled estimate of 45% (95% CI 39 to 51%) for sperm retrieval (Fig. 1).

Conclusion: In patients with NOA, micro-TESE compared with TESA may result in significantly higher sperm retrieval rate. Low certainty of evidence (GRADE ⊕⊕◯◯). The 95% CI of the reported sperm retrieval rates by micro-TESE is 39-54%.

Clinical pregnancy (Appendix 4.2)
Clinical pregnancy was reported in six case series including 3892 men with NOA. Calculated per micro-TESE procedure, the pooled clinical pregnancy rate was 20% (95% CI 15-25%). Heterogeneity was present (Fig. 2). The 95% CI for clinical pregnancy rate per successful micro-TESE ranged from 36% to 50% (Fig. 3).

Fig. 2. Meta-analysis of clinical pregnancy rate per micro-TESE procedure.

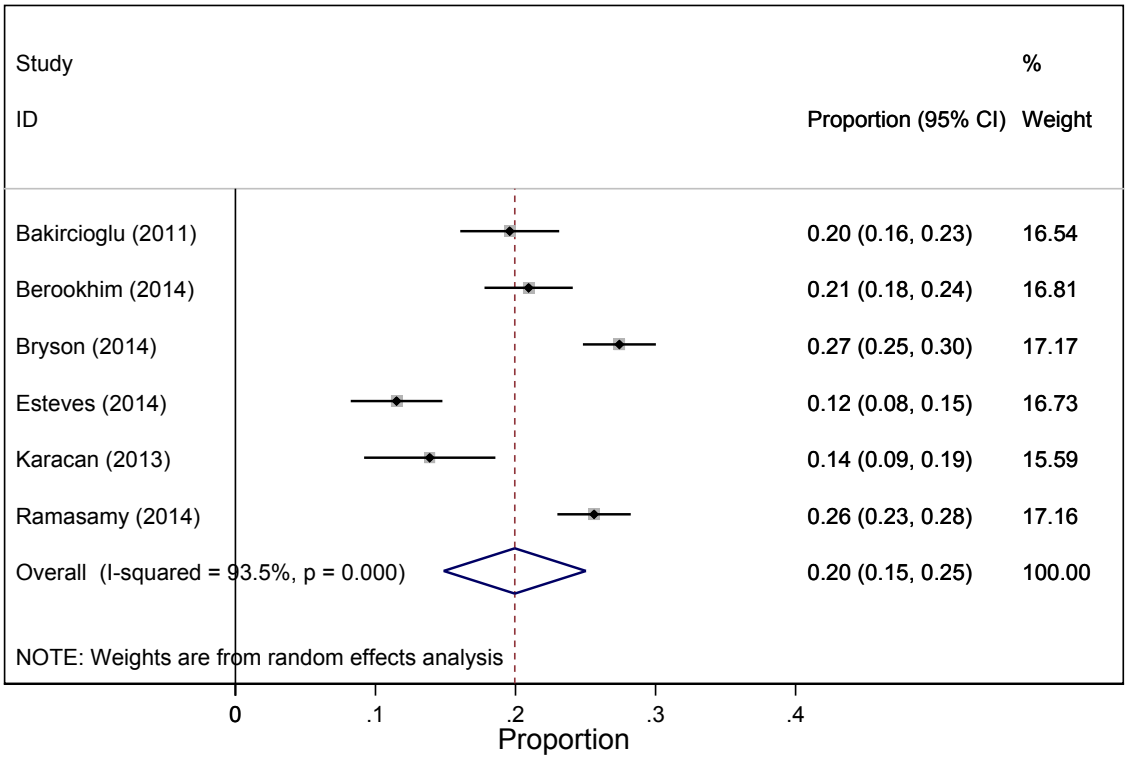
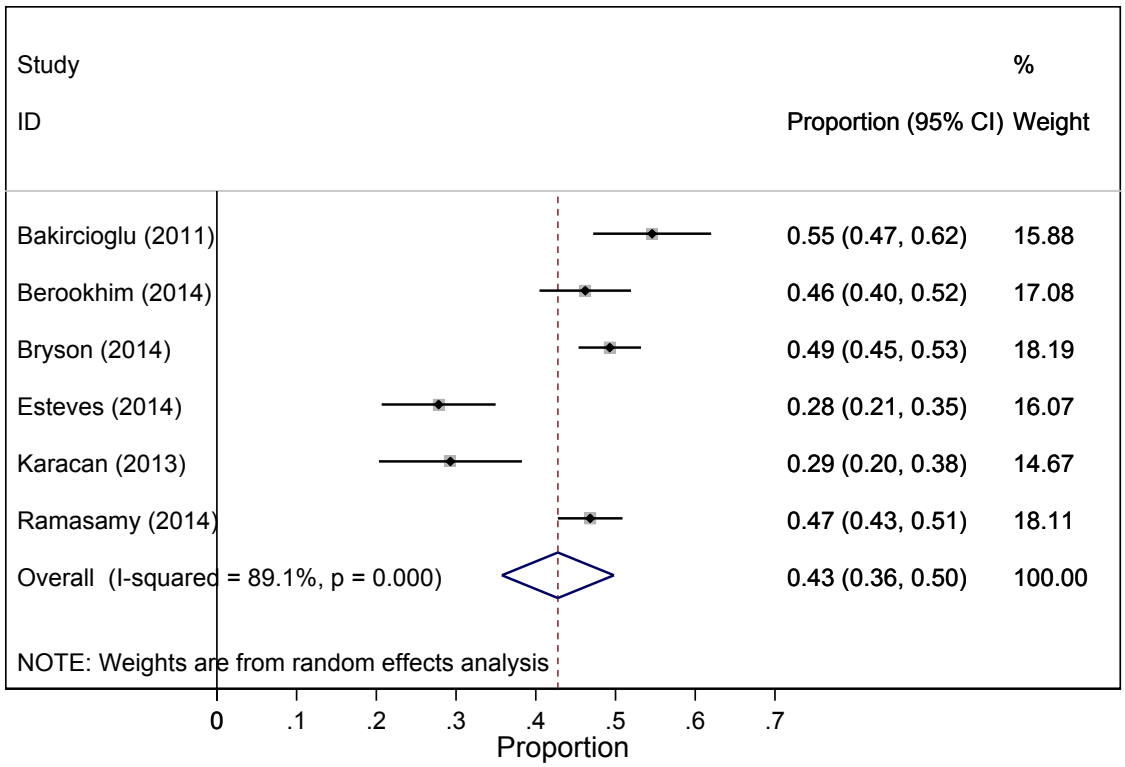


Fig. 3. Meta-analysis of clinical pregnancy rate per successful micro-TESE procedure.



Conclusion: The 95% CI for the reported clinical pregnancy rates after micro-TESE and subsequent IVF-ICSI is 15 to 25%.

Live birth (Appendix 4.3)
Live birth was reported in five case series including 3252 men with NOA. Calculated per micro-TESE procedure, the pooled live birth rate was 15% (95% CI 9 to 20%). Heterogeneity was present (Fig. 4). The 95% CI for live birth rate per successful micro-TESE ranged from 20% to 43%, (Fig. 5).

Fig. 4. Meta-analysis of live birth rate per micro-TESE procedure.

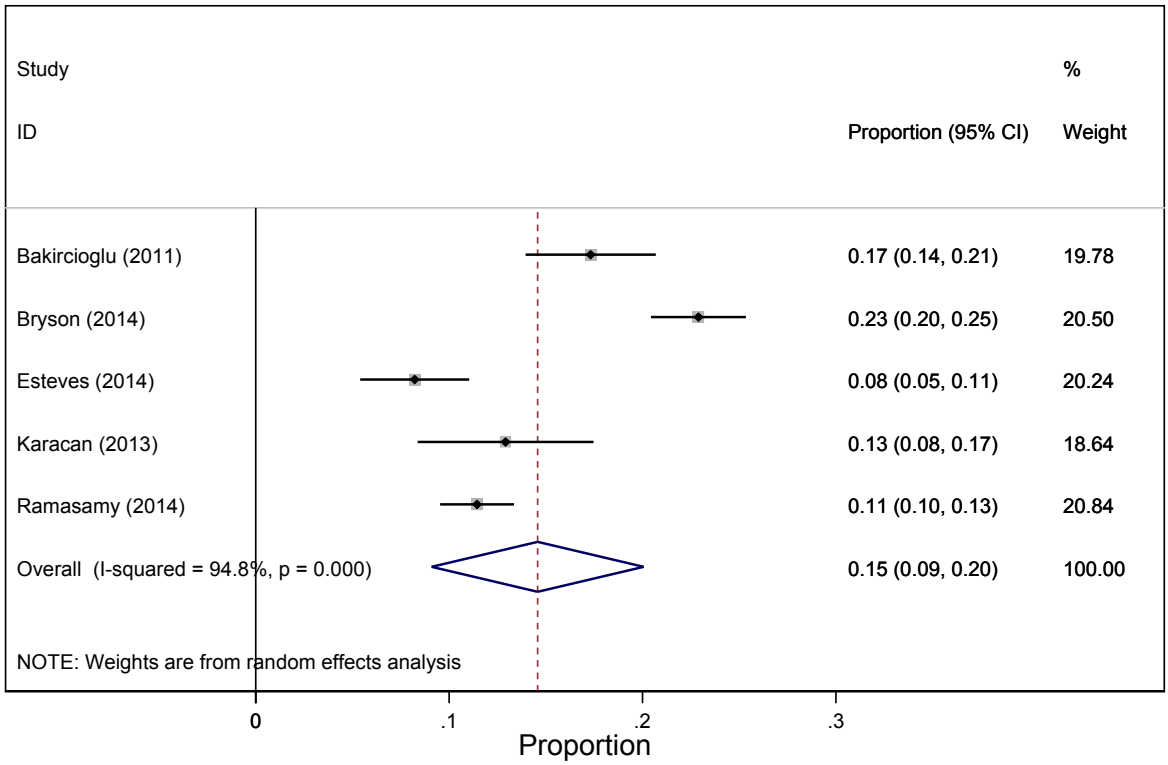
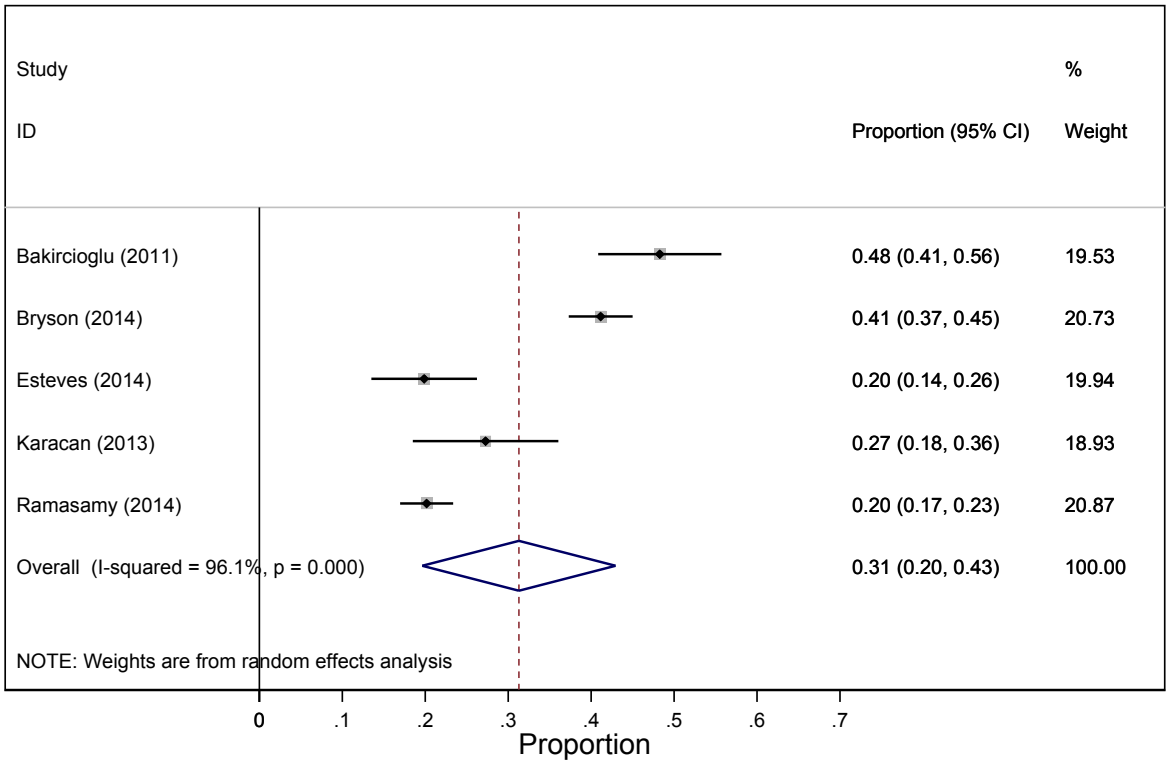


Fig. 5. Meta-analysis of live birth rate per successful micro-TESE procedure.



Conclusion: The 95% CI for reported live birth rates after micro-TESE and subsequent IVF-ICSI is nine to 20%.

Complications (Appendix 4.4)
Complications were reported in eight studies including 1563 patients with NOA. One cohort study with some study limitations and indirectness compared micro-TESE on one testicle with TESA on the other testicle in 100 patients. Ultrasound follow-up was performed at one, three and six months. No serious clinically detected complication or any surgical reinterventions were reported. Ultrasound-detected changes, mainly intra-testicular haematoma or oedema, were all resolved within two months in both groups.
Seven case series reported complications in a range from zero to nine per cent. A few cases of segmental devascularisation were described. The most common complication was intra-testicular or scrotal haematoma. No orchidectomy was reported.

Conclusion: In patients with NOA it is uncertain whether there is any difference in complication rates for micro-TESE compared with TESA (GRADE ⊕◯◯◯).

10. Ethical aspects

By introducing the Micro-TESE procedure more men with NOA would have the chance to be biological fathers to their children. It would reduce the number of couples who request sperm donation avoiding the adverse psychosocial and ethical effects of the gamete donation process. On the other hand, the micro-TESE method demands a more highly specialised staff and more time and require more resources compared with the current methods and might thus cause displacement effects.

At present infertile couples are on a waiting list some months before having access to IVF-treatment. The goal for the patient group, in accordance to national standard, is a waiting time of maximum three months. If introducing micro-TESE it might negatively affect the waiting time for all patients, since it compete with the same resources.
Some questions can be raised in this context. Should all men in whom TESA has failed be offered micro-TESE? Are male causes of infertility less well treated by the health care system than female causes?

11. Organisational aspects

Time frame for the putative introduction of the new health technology

Micro-TESE procedures were introduced in 2018 but due to lack of operating theatre resources, only three operations have been made so far at Reproductive medicine, Sahlgrenska University hospital. One severe complication among those, contributed to the initiation of this report, to define current knowledge regarding the effectiveness and safety of this method.

Present use of the technology in other hospitals in Region Västra Götaland

No other public hospital in the region offer micro-TESE. One private infertility hospital in Gothenburg (Livio Fertilitetscentrum) performs micro-TESE.

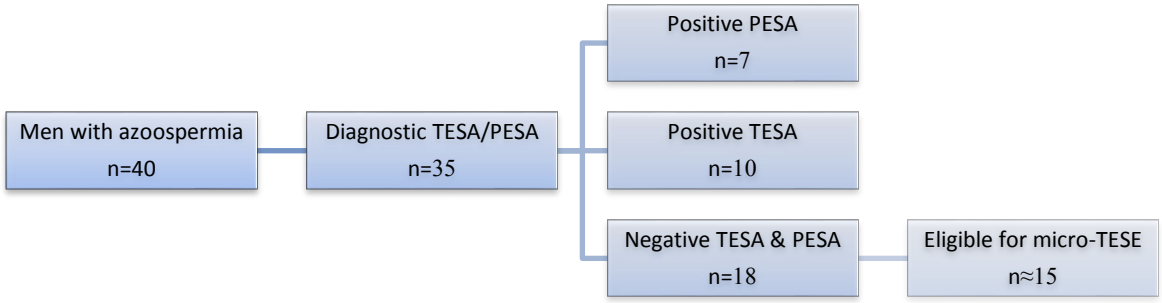
Consequences of the new health technology for personnel

The micro-TESE procedure requires a team including physicians specialised in fertility issues, midwives, assistant nurses and biomedical analysts. Our micro-TESE team has already visited two other micro-TESE centres learning the technique including teaching sessions for the different roles in this cooperative surgical procedure.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

The department of Reproduction Medicine Sahlgrenska University Hospital, Region Västra Götaland is assigned as care giver concerning infertility treatments and assisted reproductive technologies. We plan for 10-15 operations (Fig. 6) per year in our clinic. Access to an operating theatre is a new requirement compared with the TESA and PESA procedures.

Fig. 6. Men with azoospermia referred to the Reproductive Medicine Department at Sahlgrenska University Hospital for further clinical work-up during 2018.



12. Economic aspects

Present costs of currently used technologies (TESA) and expected cost of the new health technology

The cost of TESA is approximately 9,000 Swedish kronor (SEK) per intervention, whereas the cost of micro-TESE is approximately 30,000 SEK per intervention. There is an uncertainty with the latter estimate considering that the volume of micro-TESE interventions are still relatively low in a Swedish health care setting.

Expected total change in costs

The necessary technologies and resources to perform micro-TESE are available in VGR, which implies that the expected change in total costs will primarily consist of the incremental cost between micro-TESE and TESA (30,000 SEK – 9,000 SEK); 21,000 SEK multiplied by the number of interventions. With an annual patient population of 15, this will translate to an expected increase in total costs by 450,000 SEK.

What should be acknowledged is that this only refers to the short-term impact of the new technology. The long-term impact could imply further cost-increases (e.g. if micro-TESE implies an increased number of adverse events) or cost-decreases (e.g. if micro-TESE leads to a higher live birth rate and thus fewer additional interventions). However, there is currently no empirical data to substantiate if long-term cost consequences differ from the short-term impact.

Possibility to adopt and use the new technology within the present budget

The new technology will result in increased health care costs as outlined above, and there is no possibility to adopt and use the new technology within the present budget. The present budget will have to be increased or use of the new technology will lead to displacement of some other health care.

Available economic evaluations or cost advantages/disadvantages

No economic evaluations or cost-consequence or budget-impact analysis studies of the new technology was identified in the published literature.

13. Discussion

No controlled trial comparing micro-TESE and TESA for their live birth and clinical pregnancy rates was identified. The case series included in this meta-analysis reported a live birth rate (95% CI) of 9-20% and a clinical pregnancy rate (95% CI) of 15-25% per micro-TESE procedure. The success rate of sperm retrieval by micro-TESE in the only controlled cohort study in this review was about five times higher than by TESA. High sperm retrieval rates, ranging from 23% to 58%, were also reported in the case series using micro-TESE. These results might indicate a better chance of sperm retrieval using the micro-TESE method. Regarding complications of micro-TESE, the controlled cohort study showed a lower frequency of ultrasound-detected complications for micro-TESE compared with TESA. No serious complications were reported in any of the groups and all ultrasound-visible changes resolved within a couple of months. The retrospective studies reported complications ranging from zero to nine percent, mostly intra-testicular or scrotal hematomas that resolved without reoperation. No postoperative acute testicular necrosis or need of orchiectomy have been reported following micro-TESE.

There is a lack of controlled prospective studies comparing micro-TESE with no intervention and with TESA respectively. We identified only one controlled cohort study limiting the certainty of evidence. The only controlled cohort study reported sperm retrieval rate and complications to different sides within the individuals, but live birth and clinical pregnancy rates were not possible to calculate in this design. Therefore, only retrospective case series were available for analysing data on live birth and clinical pregnancy rates.

The sperm retrieval rate by micro-TESE may be considered acceptable (95% CI 39-51%) and serious complications are very infrequent. The estimated live birth rate per micro-TESE procedure is however low and this is the most important variable both for the couples seeking help and for the health care providers. It is still unclear if micro-TESE gives men with NOA a better chance to be biological father than previous methods such as TESA or conventional TESE. Microsurgical testicular sperm extraction is a more expensive treatment that requires more staff resources and will, if the budget is not increased accordingly, lead to the displacement of other health care services. However, due to the low number of men that would be considered per year, any displacement effect would be small. It is of great importance to analyse possible benefits of micro-TESE over previously used methods in further clinical trials.

14. Future perspectives

Scientific knowledge gaps

Large prospective controlled studies comparing micro-TESE with TESA or conventional TESE are needed to compare the effectiveness of micro-TESE for the outcomes sperm retrieval, clinical pregnancy live birth, and complications. So far, no study has been able to identify prognostic marker/variable for finding sperms by micro-TESE.

Ongoing research

Searching for ongoing research related to our PICO resulted in three ongoing clinical trials of relevance. One Danish randomised controlled trial (RCT) including 110 men with NOA, compares micro-TESE with TESA, for several outcomes including sperm retrieval, clinical pregnancy, live birth, and complications. Another RCT from France including 220 men with NOA, compares micro-TESE with conventional TESE and will report sperm retrieval rate only. The third RCT is being conducted in Egypt. It compares micro-TESE with conventional TESE and will report sperm retrieval, complications and a prediction model.

15. Participants in the project

The question was nominated by
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Participating healthcare professionals
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Administrative support
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Declaration of interests
No conflicts of interests to declare.

Project time
The HTA was accomplished during the period May 3rd to June 12th 2019.
Literature searches were made in March 2019.

Appendix 1: PICO, study selection, search strategies, and references

Question at issue:
Is micro-surgical TESE, compared with TESA, in men with non-obstructive azoospermia safe and effective regarding sperm retrieval, clinical pregnancy and live birth rates? After a failed TESA, is micro-TESE sufficiently effective and safe?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO 1

P	Men with non-obstructive azoospermia with absence of sperm after a previous TESA
I	Micro-TESE
C	No intervention (excluded donated sperm)
O	**Critical for decision-making** Sperm yield (yes/no) **Important for decision-making** Clinical pregnancy Live birth Complications Re-operations

PICO 2

P	Men with non-obstructive azoospermia without a previous TESA attempt
I	Micro-TESE
C	TESA
O	**Critical for decision-making** Sperm yield (yes/no) **Important for decision-making** Clinical pregnancy Live birth Complications Re-operations

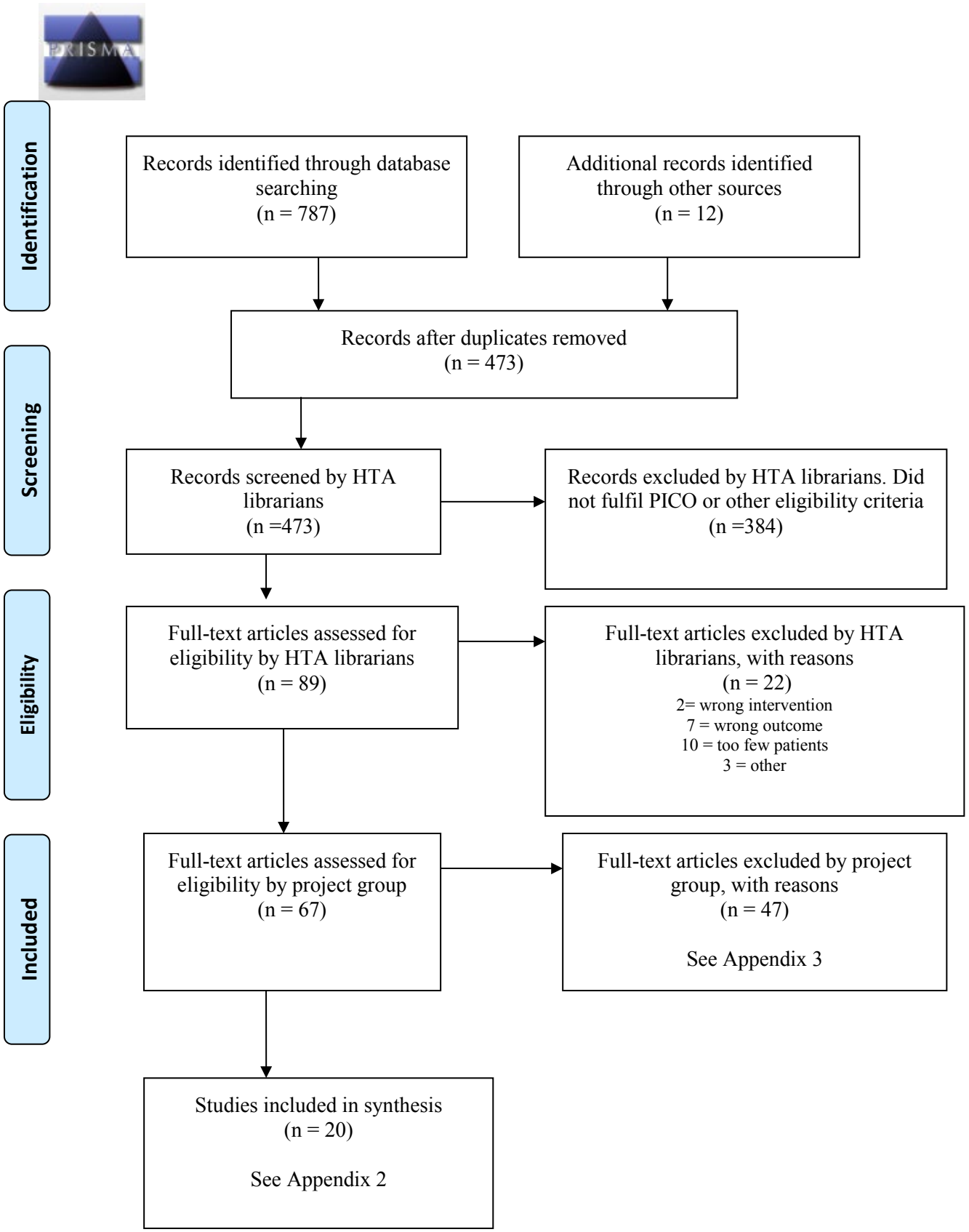
<u>Eligibility criteria</u>

Study design:
Systematic reviews
Randomised controlled trials
Non-randomised controlled studies, 10 patients in each group
Case series if ≥ 300 patients
Case series if ≥100 patients for complications

Language:
English, Swedish, Norwegian, Danish

Publication date: 1999-

Selection process – flow diagram



Modified from Moher et al., 2009

Search strategies

Database: PubMed
Date: March 7, 2019
No. of results: 369

Search	Query	Items found
#18	**Search #10 NOT #11 Filters: Publication date from 1999/01/01; Swedish; Norwegian; English; Danish**	**369**
#13	Search #10 NOT #11 Filters: Publication date from 1999/01/01	411
#12	Search #10 NOT #11	460
#11	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1701113
#10	Search #6 NOT #9	482
#9	Search #7 OR #8	4858545
#8	Search animal[ti] OR animals[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR rodent[ti] OR rodents[ti] OR dog[ti] OR dogs[ti] OR cat[ti] OR cats[ti] OR hamster[ti] OR hamsters[ti] OR rabbit[ti] OR rabbits[ti] OR swine[ti] OR horse[ti] OR horses[ti] OR buffalo[ti] OR boar[ti] OR boars[ti] OR ram[ti] OR rams[ti] OR frog[ti] OR frogs[ti]	1798806
#7	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4554383
#6	Search #3 OR #4 OR #5	508
#5	Search testicular tissue microdissection OR testicular tissue micro-dissection	93
#4	Search micro-TESE OR microTESE OR mTESE OR m-TESE OR MDTESE OR MD-TESE	172
#3	Search #1 AND #2	426
#2	Search testicular sperm extraction OR TESE OR sperm retrieval OR Sperm Retrieval [MeSH] OR testicular extraction of spermatozoa OR sperm extraction	3702
#1	Search micro-dissection OR microdissection OR micro-surgical OR microsurgical	26297

Database: Embase 1974 to 2019 March 06 (OvidSP)
Date: March 7, 2019
No. of results: 393

#	Searches	Results
1	(micro-dissection or microdissection or micro-surgical or microsurgical).af.	35666
2	((testicular adj4 sperm adj4 extraction) or TESE or (sperm adj4 retrieval) or (testicular adj4 extraction adj4 spermatozoa) or (sperm adj4 extraction)).af.	4095
3	sperm retrieval/ or exp testicular sperm extraction/	2360
4	2 or 3	4095
5	1 and 4	781
6	(micro-TESE or microTESE or mTESE or m-TESE or MDTESE or MD-TESE).af.	476
7	((testicular adj4 tissue adj4 microdissection) or (testicular adj4 tissue adj4 micro-dissection)).af.	7
8	5 or 6 or 7	927
9	(animal not (animal and human)).sh.	1029141
10	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or horse or horses or buffalo or boar or boars or ram or rams or frog or frogs).ti.	1871623
11	9 or 10	2654000
12	8 not 11	916
13	limit 12 to ((embase or medline) and (article or article in press or conference paper or note or "review" or short survey))	497
14	**limit 13 to ((danish or english or norwegian or swedish) and yr="1999 -Current")**	**393**

Database: The Cochrane Library
Date: March 7, 2019
No. of results: 25
Cochrane reviews 1
Cochrane protocols 0
Trials 24
Other reviews 0

ID	Search	Hits
#1	(micro-dissection OR microdissection OR micro-surgical OR microsurgical):ti,ab,kw (Word variations have been searched)	502
#2	(testicular sperm extraction OR TESE OR sperm retrieval OR testicular extraction of spermatozoa OR sperm extraction):ti,ab,kw (Word variations have been searched)	813
#3	MeSH descriptor: [Sperm Retrieval] explode all trees	13
#4	#2 OR #3	813
#5	#1 AND #4	22
#6	(micro-TESE OR microTESE OR mTESE OR m-TESE OR MDTESE OR MD-TESE):ti,ab,kw (Word variations have been searched)	8
#7	(testicular tissue microdissection OR testicular tissue micro-dissection):ti,ab,kw (Word variations have been searched)	3
#8	**#5 OR #6 OR #7**	**25**

The web-sites of **SBU** and **Folkehelseinstituttet** and NICE were visited March 7, 2019. Nothing relevant to the question at issue was found.

Reference lists
A comprehensive review of reference lists brought 12 new records

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Project: Effectiveness and safety of microsurgical testicular sperm extraction
Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Study Duration (years) NOA subgroup	Study Groups; Intervention vs control	Patients (n)	Outcome variables
Althakafi 2017 Saudi Arabia	Case series PICO 2	2009-2015	Micro-TESE	421	Sperm retrieval
Amer 2019a Egypt	Case series PICO 2	2017-2018	Micro-TESE	1395	Sperm retrieval
Amer 2019b Egypt	Case series PICO 2	2017-2018	Micro-TESE	330	Sperm retrieval
Amer 2000 Egypt	Case series PICO 2	Not reported	Micro-TESE	100	Sperm retrieval Complications
Bakircioglu 2011 Turkey	Case series PICO 2	2004-2008	Micro-TESE	106 KS 379 NOA	Sperm retrieval Clinical pregnancy Live birth
Berookhim 2014 USA	Case series PICO 2	199-2013 Sertoli cell	Micro-TESE	640	Clinical pregnancy Sperm retrieval
Binsaleh 2017 Saudi Arabia	Case series PICO2	2011-2014	Micro-TESE	255	Sperm retrieval Complications
Bryson 2014 USA	Case series PICO 2	1999-2011	Micro-TESE	1127	Sperm retrieval Clinical pregnancy Live birth
Dardashti 2000 USA	Case series PICO2	Start1988, finish not reported.	Micro-TESE	119	Complications
El-Haggar 2008 Egypt	Cohort PICO 2 (comparison between sides)	Not reported	Micro-TESE vs FNA (TESA)	100	Sperm retrieval Complications
Enatsu 2016 Japan	Case series PICO 2	Not reported	Micro-TESE	329	Sperm retrieval
Esteves 2014 USA	Case series PICO 2	Not reported (study period 7 year)	Micro-TESE	365	Sperm retrieval Clinical pregnancy Live birth Complications
Ishikawa 2010 Japan	Case series PICO2	Start 2006, finish not reported.	Micro-TESE	150	Sperm retrieval Complications
Karacan 2013 Turkiet	Case series PICO 2	2006-2012	Micro-TESE	406 (see results)	Sperm retrieval Clinical pregnancy Live birth (delivery rate) Complications

Project: Effectiveness and safety of microsurgical testicular sperm extraction
Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Study Duration (years) NOA subgroup	Study Groups; Intervention vs control	Patients (n)	Outcome variables
Kizilay 2019 Turkey	Case series PICO 2	2016-2018	Micro-TESE	346	Sperm retrieval
Klami 2018 Finland	Case series PICO2	2008-2015	Micro-TESE	100	Sperm retrieval Complications
Ramasamy 2014 USA	Case series PICO 2	Age factors 1999-2010	Micro-TESE	1066	Sperm retrieval Clinical pregnancy Live birth
Ramasamy 2005 USA	Case series PICO 2	Not reported	Micro-TESE	435	Complications
Sabbaghian 2014 Iran	Case series PICO 2	2009-2012	Micro-TESE	137 KS 537 NOA	Sperm retrieval
Turunc 2016 Turkey	Case series PICO 2	2004-2014 Learning curve	Micro-TESE	300	Sperm retrieval

FNA=fine needle aspiration (TESA procedure), Micro-TESE=, Microsurgical Testicular Sperm Extraction, KS= Klinefelter syndrome, NOA= Non-Obstructive Azoospermia, TESA= Testicular Sperm Aspiration

Project: Effectiveness and safety of microsurgical testicular sperm extraction
Appendix 3. Excluded articles

Author, year	Reason for exclusion
Amer 2008	N=64, no complications reported.
Arafa 2015	N=115, no complications reported.
Aydin 2015	N=111, no complications reported.
Aydos 2005	Evaluating other methods, no complications reported.
Bernie 2015b	N=211,No complications reported
Bernie 2015a	Wrong comparisons (cTESE vs TESA, cTESE vs mTESE)
Caroppo 2019	N=143, no complications reported
Cetinkaya 2015	N=191, no complications reported
Cherhazi 2017	Double publication with Sabbaghian
Corona 2017	Wrong comparison (cTESE vs mTESE)
Eken 2018	N=145, no complications reported
Elnaser 2004	N=168, no complications reported
Erdem 2018	N=225, no complications reported
Erdem 2017	Case series with too few NOA patients (251)
Flannigan 2019	Non-systematic review with focus on surgical techniques
Hibi 2005	Mixed intervention, mTESE not reported separately
Ishikawa 2009	N=140, no complications reported
Iwatsuki 2017	N=217, no complications reported
Jensen 2016	Retrospective cohort but for our purpose a case series, PICO 1. Too few patients, n=126 NOA
Kalsi 2012	Case series with too few patients (n=100)
Karamazak 2018	N=282, no complications reported
Madbouly 2008	N=100, no complications reported. 15 patinets with TESA earlier performed (pico1), few numbers.
Modaresi 2013	Almost a copy of Aydos 2004, evaluating other methods. Micro-TESE not specifically reported. N = 150 Complications not reported.
Ozer 2018	N=110, no complications reported
Ramasay 2011a	Wrong focus, duration of procedure. Double publication.
Ramasamy 2011b	Wrong focus, laboratory vs OR room sperm retrieval. Double publication.
Ramasamy 2011c	N=126, no complications reported
Ramasamy 2013a	Wrong focus, overweight. Double publication.
Ramasamy 2013b	Wrong focus, additional yield from contralateral testis. Double publication.
Ramasamy 2009	Wrong focus, FSH levels. Double publication.
Ramasamy 2007	Wrong focus, influence of prior biopsy. Double publication.
Reifsnyder 2012	Double publication
Rohayem 2015	N=135, no complications reported
Sajadi 2019	Double publication
Salehi 2017	N=170, no complications reported
Schwartzer 2013	N=220, no complications reported
Shah 2018	Systematic review, no additional information

Project: Effectiveness and safety of microsurgical testicular sperm extraction
Appendix 3. Excluded articles

Author, year	Reason for exclusion
Stahl 2010	Double publication
Takeda 2017	N=197, no complications reported
Wald 2006	No m-TESE, only results from TESE and MESA. No complications reported.
Tsujimura 2004	Looking for prediction formula
Tsujimura 2005	Looking for prediction model
Yildirim 2014	N=131, no complications reported
Yucel 2019	Double publication with Kizilay
Yumura 2018	No reporting on type of male infertility
Zhang 2013	N=170, no complications reported
Zhang 2018	N=120, no complications reported

Project: Effectiveness and safety of microsurgical testicular sperm extraction (PICO 2; micro-TESE vs TESA)
Appendix 4.1
Outcome variable: Sperm retrieval

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention: Micro-TESE n/n (%)	Control: TESA n/n (%)				
El-Haggar 2008 Egypt	Cohort	100 NOA		52/100 (52)	10/100 (10)		?	?	?
Althakafi 2017 Saudi Arabia	Case series	421 NOA		166/421 (39.4)					
Amer 2000 Egypt	Case series	118 NOA		62/118 (53)					
Amer 2019a Egypt	Case series	1395 NOA		450/1395 (32)					
Bakircioglu 2011 Turkey	Case Series	106 KS 379 NOA		50/106 (47) 188/379 (50)					
Berookhim 2014 USA	Case series	640 NOA		285/640 (44.5)		Sertoli cell-only patients			
Bryson 2014 USA	Case series	1127 NOA		631/1127 (56)					
Enatsu 2016 Japan	Case series	329 NOA		97/329 (29.5)					
Esteves 2014 Brazil	Case series	365 NOA		151/365 (41)					
Ishikawa 2010 Japan	Case series	150 NOA		1st 50 patients: 16/50 (32) 2nd 50 patients: 22/50 (44) 3rd 50 patients: 24/50 (48)		Patients were divided in three groups to evaluate the influence of surgeons' experience on sperm retrieval outcome.			
Karacan 2013 Turkey	Case series	406 NOA		223/406 (55)		Seems that they have included repeated cases.			
Kizilay 2019 Turkey	Case series	346 NOA		1st: 141/244 (57.8) 2nd : 30/73 (41.1) 3rd : 6/29 (20.7)					

Project: Effectiveness and safety of microsurgical testicular sperm extraction (PICO 2; micro-TESE vs TESA)
Appendix 4.1
Outcome variable: Sperm retrieval

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention: Micro-TESE n/n (%)	Control: TESA n/n (%)				
Klami 2018 Finland	Case series	100		42/100 (42)					
Ramasamy 2014 USA	Case series	1066		605/1066 (56.7)					
Sabbaghian 2014 USA	Case series	134 KS 537 NOA		38/134 (28.4) KS 119/537 (22.2) NOA					
Turunc 2016 Turkey	Case series	300 NOA		141/300 (47%)					

KS= Klinefelter syndrome, m-TESE=, Microsurgical Testicular Sperm Extraction, NOA= Non-Obstructive Azoospermia, SR=sperm retrieval rate, TESA= Testicular Sperm Aspiration

Project: Effectiveness and safety of microsurgical testicular sperm extraction (PICO 2; micro-TESE vs TESA)
Appendix 4.2
Outcome variable: Clinical pregnancy

* + No or minor problems
? Some problems
\- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results				Comments
				Intervention: Micro-TESE		Control: TESA		
				Pregnancy/ m-TESE n/n (%)	Pregnancy/ successful m-TESE n/n (%)	Pregnancy/ TESA n/n (%)	Pregnancy/ successful TESA n/n (%)	
Bakircioglu 2011 Turkey	Case series	106 KS 379 NOA		26/106 (24.5) 69/379 (18.2)	26/49 (53.1) 69/125 (55.2)	-	-	
Berookhim 2014 USA	Case series	640 NOA		134/640 (20.9)	134/290 (46.2)	-	-	"Sertoli-cell only" patients
Bryson 2104 USA	Case series	1127 NOA		309/1127 (27.4)	309/627 (49.3)	-	-	
Esteves 2014 USA	Case series	365 NOA		42/365 (11.5)	42/151 (27.8)	-	-	
Karacan 2013 Turkey	Case series	209 NOA		29/209 (13.9)	29/99 (29)	-	-	
Ramasamy 2014 USA	Case series	1066 NOA		265/1023 (25.9) 8/43 (18.6)	a: 265/552 (48) b: 8/31 (25)			a: men<50 years n=1023 b: men > 50 years n =43 Klinefelter syndrome excluded

KS= Klinefelter syndrome, m-TESE=, Microsurgical Testicular Sperm Extraction, NOA= Non-Obstructive Azoospermia, SR=sperm retrieval rate, TESA= Testicular Sperm Aspiration

Project: Effectiveness and safety of microsurgical testicular sperm extraction (PICO 2; micro-TESE vs TESA)
Appendix 4.3
Outcome variable: Live birth

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results				Comments
				Intervention: Micro-TESE		Control: TESA		
				Live birth/ m-TESE n/n (%)	Live birth/ successful m-TESE n/n (%)	Live birth/ TESA n/n (%)	Live birth/ successful TESA n/n (%)	
Bakircioglu 2011 Turkey	Case series	106 KS 379 NOA	0	KS 23/106 (21.7) NOA 61/379 (16.1)	KS 23/49 (46.9) NOA 61/125 (48.8)	-	-	
Bryson 2014 USA	Case series	1127 NOA	0	258/1127 (22.9)	258/627 (41.1)	-	-	
Esteves 2014 USA	Case series	365	0	30/365 (8.2)	30/151 (19.9)	-	-	
Karacan 2013 Turkey	Case series	337 NOA 209 OA 128	0	NOA 27/209 (12.9)	NOA 27/99 (27)	-	-	
Ramasamy 2014 USA	Case series	1066	0	122/1066 (11.4)	122/605 (20.2)	-	-	

KS= Klinefelter syndrome, m-TESE=, Microsurgical Testicular Sperm Extraction, NOA= Non-Obstructive Azoospermia, SR=sperm retrieval rate, TESA= Testicular Sperm Aspiration

Project: Effectiveness and safety of microsurgical testicular sperm extraction (PICO 2; micro-TESE vs TESA)
Appendix 4.4
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention: Micro-TESE	Control: TESA				
El-Haggar 2008 Egypt	Cohort	100 NOA		Intratesticular hematoma 4/100 (4%) Intratesticular oedema 2/100 (2%) Localized devascularisation 2/100 (2%) Tunical interruption 2/100 (2%) Total 10/100 (10%)	Intratesticular hematoma 14/100(14%) Haematocele 2/100 (2%) Bruise of scrotal skin 6/100 (6%) Total 22/100 (22%), p=0.034	Comparison of sides All complications were resolved at two months in both groups	?	?	-
Amer 2000 Egypt	Cases series	60 NOA		Intratesticular haematoma 9/60 (15%) but no scrotal haematoma. Focal lesion (fibrosis) 2/60 (3%)		These finding are verified by ultrasound-assisted examination during 6-month follow up.			
Binsaleh 2017 Saudi Arabia	Cases series	255 NOA		No intraoperative complications. Postoperative complications 2/225 (0.88%),	-	In text: Postop complication one scrotal oedema, one surgical site infection. None required surgical intervention.			
Dardashti 2000 USA	Case series	107		No scrotal hematoma No testicular atrophy 0/107					
Iskikawa 2010 Japan	Cases series	150 NOA		0/150		(3 groups: 50 + 50 +50) In text: no patient had postoperative complications.			
Karacan 2013 Turkey	Cases series	337 NOA		3/337 (0.9%)		In text: 3 patients with acute scrotal hematoma, which disappeared within a few days. No severe complications.			
Klami 2018 Finland	Cases series	100 NOA		9/100 (9%)		2 epididymitis (oral antibiotics) 4 unspecified infections (oral antibiotics) 2 haematomas (expectation) 1 abscess (surgical treatment)			
Ramasamy 2005 USA	Cases series	435		Acute ultrasound findings 36/82 (44%) Segmental devascularisation 4/82 (5%)		Ultrasound and endocrine evaluation TESE vs micro-TESE postoperative 3-6 month			

KS= Klinefelter syndrome, m-TESE=, Microsurgical Testicular Sperm Extraction, NOA= Non-Obstructive Azoospermia, SR=sperm retrieval rate, TESA= Testicular Sperm Aspiration

Project: Effectiveness and safety of microsurgical testicular sperm extraction
Appendix 5. Ethical aspects

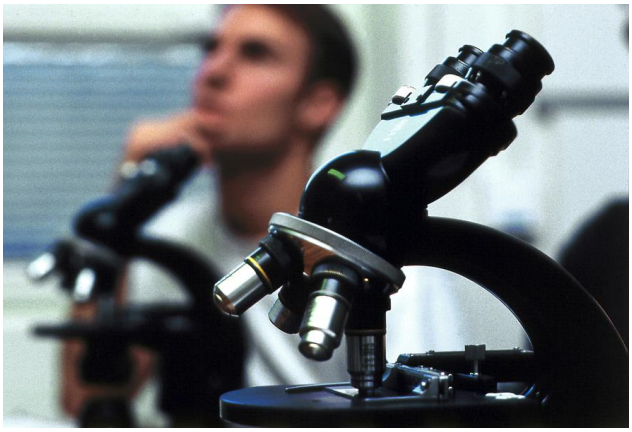
The effect of the intervention on health	
Q1: Health: How does the intervention effect patients' health in terms of quality of life and life-length (including adverse effects)?	**A successful procedure can gives the patient chance of livebirth of an offspring. If not successful, the patient would not be able to be a biological father to any child.**
Q2: Knowledge gaps: If there is lack of scientific evidence for the effect of the intervention, are there ethical and/or methodological problems with future research in order to strengthen this evidence.	**-**
Q3: Degree of severity: What degree of severity has the condition the intervention is supposed to treat?	**Depending to the outcome can this intervention give results as pregnancy, childbirth or no fertility at all.**
Q4: Third parties: How does the intervention affect the health of third parties?	**Succes or failure of this intervention affects patients partner both physically and psychologically.**
Summary: How is the benefit/risk – ration for the intervention (given the answers of Q1-Q4)?	**The major benefit is childbirth and the risks are those known surgical complication and eventually psychological effects on patient with unsuccessful intervention lifelong.**
Q5: Equality and justice: Is there a risk that access to the intervention violates the Human Dignity principle or the Swedish Discrimination Act?	**No**
The compatibility of the intervention with ethical values	
Q6: Autonomy: Can the intervention affect patients' and significant others participation in decisions and there ability to make informed and relevant decisions about the intervention?	**Yes**
Q7: Privacy: How does the intervention affect patient's and significant others' physical and personal privacy?	**??**
Q8: Cost effectiveness: Is the balance between the cost and effects of the intervention reasonable?	**We believe so.??**
Summary: Is the use of the intervention compatible with ethical values (given the answers of Q5-Q8)?	**Yes**

Project: Effectiveness and safety of microsurgical testicular sperm extraction
Appendix 5. Ethical aspects

Structural factors that can affect the use and consequences of the intervention	
Q9: Resources and organisation: Are there resource- or organizational limitations that can affect who will get access to the intervention or that can lead to less access to other care if the intervention is used?	**This intervention can only be used for selected patients and requires more resources though the organization compared to the other older methods. This might influence the other couples waiting time to other kinds of infertility treatment. This influence is going to be minimal by arranging this intervention by special occasions.**
Q10: Professional values: Can values within the affected care professions influence the use of the intervention and thereby lead to unequal access?	**Hopefully not.**
Q11: Stake holder interests: Are there stake holder interests that can influence the use of the intervention and thereby lead to unequal access?	**No**
Summary: Are there reason to believe that an equal access to the intervention (or other care interventions) can be affected (given the answers to Q9-Q11)?	**No**
Long-term ethical consequences	
Q12: Long-term consequences: Can the use of the intervention result in more long-term consequences?	**No**
Overall summary	
How can the ethical aspects regarding the intervention be summarised? Does this summary indicate that the intervention should be modified or that there should be special requirements associated with offering the intervention?	Plussida för paret att få egna biologiska barn. Minussidan kostnad för samhället, ganska låg frekvens av framgång. Många behöver op för att hitta de som har tillgängliga spermier. ”Last chance”

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
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