National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

[T] Y chromosome microdeletion

NICE guideline NG257

Evidence reviews underpinning recommendations 1.17.7 and 1.26.1 in the NICE guideline

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Final

Developed by NICE

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Y chromosome microdeletion

Review question

What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

Introduction

The human Y chromosome has genetic material responsible for normal testis development and sperm production (spermatogenesis). Small genetic deletions on the Y chromosome, known as Y chromosome microdeletions, are associated with the absence of sperm in ejaculate (non-obstructive azoospermia) or severely low sperm count (severe oligozoospermia). Y chromosome microdeletions are the second most common genetic cause of male fertility after Klinefelter syndrome, and there are three commonly identified Y chromosome microdeletions, known as azoospermia factor a (AZFa), azoospermia factor b (AZFb) and azoospermia factor c (AZFc) microdeletions. People with Y chromosome microdeletions often require surgical sperm retrieval and assisted reproductive technology (ART) for fertility. Surgical sperm retrieval rate may be different in people with AZFa, AZFb and AZFc microdeletions, and understanding sperm retrieval rate in these populations can be useful in deciding appropriate treatment plan. This review aims to summarise evidence from observational studies investigating the predictive value of AZFa, AZFb and AZFc microdeletions for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia.

Summary of the protocol

Table 1: Summary of the protocol

Population	Inclusion: • People with fertility problems associated with non-obstructive azoospermia or severe oligozoospermia Exclusion: • Management of recurrent miscarriage
Prognostic factors	• Y chromosome microdeletion testing for azoospermia factors (AZF) microdeletion ○ AZFa ○ AZFb ○ AZFc
Comparison	• Head-to-head comparison between AZFa, AZFb, and AZFc • No Y chromosome microdeletion
Outcome	**Critical** • Sperm retrieval rate by surgical intervention (as defined by study, risk of bias assessments will reflect where this is not defined as sperm suitable for ICSI)

AZF: azoospermia factor; ICSI: intracytoplasmic sperm injection

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are

described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Prognostic evidence

Included studies

Thirty-nine studies were included for this review, 8 prospective cohort studies (Abur 2019; Brandell 1998; Guneri 2016; Iwahata 2017; Kihaile 2004; Mascarenhas 2016; Miraghazadeh 2019; Simoni 2008), and 31 retrospective cohort studies (Arafa 2018; Cetinkaya 2015; Chen 2019; Choi 2004; Choi 2013; Deng 2023; Gao 2022; Goncalves 2017; Hopps 2003; Iijima 2020; Johnson 2019; Kizilay 2019; Kizilkan 2019; Klami 2018; Ko 2016; Ku 2017; Lan 2022; Lo Giacco 2014; Mahdy 2024; Park 2013; Patrat 2010; Schwarzer 2016; Sen 2023; Silber 1998; Stahl 2010 & 2011 [1 study reported across 2 papers]; Tian 2023; Tsujimura 2004; Uzay 2021; Yamaguchi 2020; Zeadna 2020; Zhang 2021).

The included studies are summarised in Table 2.

We planned to subgroup the evidence by complete and partial AZFc microdeletion. However, 30 studies did not specify whether participants had complete or partial AZFc microdeletion (Abur 2019; Arafa 2018; Brandell 1998; Cetinkaya 2015; Chen 2019; Choi 2004; Choi 2013; Deng 2023; Goncalves 2017; Guneri 2016; Hopps 2003; Iijima 2020; Johnson 2019; Kihaile 2004; Kizilay 2019; Kizilkan 2019; Klami 2018; Ko 2016; Lan 2022; Mahdy 2024; Mascarenhas 2016; Park 2013; Patrat 2010; Schwarzer 2016; Sen 2023; Tian 2023; Uzay 2021; Yamaguchi 2020; Zeadna 2020; Zhang 2021). Three studies included participants with complete and partial AZFc microdeletion (Ku 2017; Silber 1998; Stahl 2010 & 2011), 2 studies included participants with complete AZFc microdeletion only (Iwahata 2017; Lo Giacco 2014), and 4 studies included participants with partial AZFc microdeletion only (Gao 2022; Miraghazadeh 2019; Simoni 2008; Tsujimura 2004).

Twenty-eight studies compared Y chromosome microdeletion (any) to no Y chromosome microdeletion (Abur 2019; Arafa 2018; Brandell 1998; Cetinkaya 2015; Chen 2019; Choi 2004; Choi 2013; Deng 2023; Gao 2022; Guneri 2016; Iijima 2020; Iwahata 2017; Johnson 2019; Kizilkan 2019; Klami 2018; Ko 2016; Ku 2017; Lan 2022; Mahdy 2024; Miraghazadeh 2019; Sen 2023; Silber 1998; Stahl 2010 & 2011; Tian 2023; Tsujimura 2004; Yamaguchi 2020; Zeadna 2020; Zhang 2021).

Twenty-six studies compared AZFc microdeletion (isolated) to no Y chromosome microdeletion (Abur 2019; Arafa 2018; Brandell 1998; Chen 2019; Choi 2004; Choi 2013; Gao 2022; Guneri 2016; Iijima 2020; Iwahata 2017; Johnson 2019; Kizilkan 2019; Klami 2018; Ko 2016; Ku 2017; Lan 2022; Mahdy 2024; Miraghazadeh 2019; Sen 2023; Silber 1998; Stahl 2010 & 2011; Tian 2023; Tsujimura 2004; Yamaguchi 2020; Zeadna 2020; Zhang 2021).

Sixteen studies compared AZFc microdeletion (isolated) to no chromosomal abnormality (sensitivity analysis) (Abur 2019; Arafa 2018; Chen 2019; Gao 2022; Iijima 2020; Iwahata 2017; Johnson 2019; Klami 2018; Ko 2016; Ku 2017; Lan 2022; Miraghazadeh 2019; Sen 2023; Stahl 2010 & 2011; Tian 2023; Zhang 2021).

Fifteen studies compared AZFa or AZFb microdeletion (isolated or in combination with other loci) to no Y chromosome microdeletion (Arafa 2018; Brandell 1998; Choi 2004; Choi 2013; Guneri 2016; Iijima 2020; Iwahata 2017; Johnson 2019; Ko 2016; Ku 2017; Mahdy 2024; Sen 2023; Stahl 2010 & 2011; Tsujimura 2004; Zeadna 2020).

Twenty-six studies compared AZFc microdeletion (isolated) to AZFa or AZFb microdeletion (isolated or in combination with other loci) (Arafa 2018; Brandell 1998; Choi 2004; Choi 2013;

Goncalves 2017; Guneri 2016; Hopps 2003; Iijima 2020; Iwahata 2017; Johnson 2019; Kihaile 2004; Kizilay 2019; Ko 2016; Ku 2017; Lo Giacco 2014; Mahdy 2024; Mascarenhas 2016; Park 2013; Patrat 2010; Schwarzer 2016; Sen 2023; Simoni 2008; Stahl 2010 & 2011; Tsujimura 2004; Uzay 2021; Zeadna 2020).

Twenty-four studies defined sperm retrieval rate by surgical intervention as sperm suitable for intracytoplasmic sperm injection (ICSI) (Abur 2019; Arafa 2018; Brandell 1998; Chen 2019; Choi 2004; Choi 2013; Gao 2022; Goncalves 2017; Hopps 2003; Johnson 2019; Kihaile 2004; Klami 2018; Ko 2016; Lan 2022; Lo Giacco 2014; Patrat 2010; Schwarzer 2016; Silber 1998; Simoni 2008; Stahl 2010 & 2011; Tian 2023; Uzay 2021; Yamaguchi 2020; Zhang 2021), but 15 studies did not specify whether sperm was suitable for ICSI (Cetinkaya 2015; Deng 2023; Guneri 2016; Iijima 2020; Iwahata 2017; Kizilay 2019; Kizilkan 2019; Ku 2017; Mahdy 2024; Mascarenhas 2016; Miraghazadeh 2019; Park 2013; Sen 2023; Tsujimura 2004; Zeadna 2020).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Prognostic factor comparisons	Outcomes	Comments
Abur 2019 Prospective cohort study Turkey	N=94 Non-obstructive azoospermia AZFc microdeletion: 15 No chromosomal abnormality: 79 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Arafa 2018 Retrospective cohort study Qatar	N=225 Azoospermia or severe oligozoospermia (proportion NR) AZFc microdeletion: 3 AZFb and c microdeletion: 2	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: TESE

Study	Population	Prognostic factor comparisons	Outcomes	Comments
	No Y chromosome microdeletion (included other chromosomal abnormalities): 220 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis) • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)		The no Y chromosome microdeletion group included n=191 with idiopathic infertility (surgical sperm retrieval rate in this group: 111/191) and n=29 with chromosomal abnormalities other than Y chromosome microdeletions (including n=19 with KS)
Brandell 1998 Prospective cohort study USA	N=80 Azoospermia AZFc microdeletion: 2 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 3 AZFb microdeletion: 3 No Y chromosome microdeletion (other chromosomal abnormalities NR): 71 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: TESE
Cetinkaya 2015 Retrospective cohort study	N=191 Non-obstructive azoospermia AZFc microdeletion: 5	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion

Study	Population	Prognostic factor comparisons	Outcomes	Comments
Turkey	AZFa, b and c microdeletion: 1 AZFa and c microdeletion: 1 AZFb and c microdeletion: 2 AZFb microdeletion: 1 No Y chromosome microdeletion (included other chromosomal abnormalities): 181 Male age in years, mean (SD): 34.4 (5.6) Duration of infertility in years; mean (SD): 7.8 (5.1)			Surgical sperm retrieval method: micro-TESE Disaggregated outcome data (based on loci of Y chromosome microdeletion) was not reported The no Y chromosome microdeletion group included n=175 with normal karyotypes (disaggregated sperm retrieval rate in this group not reported) and n=6 with KS
Chen 2019 Retrospective cohort study China	N=595 Non-obstructive azoospermia AZFc microdeletion: 34 No Y chromosome microdeletion (included other chromosomal abnormalities): 561 Male age in years; mean (SD): 29.4 (6.2) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE The no Y chromosome microdeletion group included n=446 with idiopathic infertility (surgical sperm retrieval rate in this group: 119/446), n=66 with KS, n=33 with undescended testes, n=13

Study	Population	Prognostic factor comparisons	Outcomes	Comments
				post-infectious disease, and n=3 post-gonadotoxic treatment
Choi 2004 Retrospective cohort study USA	N=34 (36 cycles) Non-obstructive azoospermia AZFc microdeletion: 6 (7 cycles) AZFb and c microdeletion: 2 (complete) AZFb microdeletion: 2 (1 complete, 1 partial) AZFa microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 23 (24 cycles) Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: TESE SSR rate denominator reported as ICSI cycles
Choi 2013 Retrospective cohort study Korea	N=112 Non-obstructive azoospermia AZFc microdeletion microdeletion: 21 AZFb and c microdeletion: 9 No Y chromosome microdeletion (other chromosomal abnormalities NR): 82 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: multiple-TESE

Study	Population	Prognostic factor comparisons	Outcomes	Comments
		combination with other loci)		
Deng 2023 Retrospective cohort study China	N=200 Non-obstructive azoospermia Y chromosome microdeletion (loci NR): 21 No Y chromosome microdeletion (included other chromosomal abnormalities): 179 Male age in years; mean (SD): NR (median 31, IQR 29-33) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE The no Y chromosome microdeletion group included n=128 with idiopathic infertility (surgical sperm retrieval rate in this group: 35/128), n=24 with KS, n=15 with undescended testes, n=10 post-infectious disease, and n=2 post-gonadotoxic treatment
Gao 2022 Retrospective cohort study China	N=335 Non-obstructive azoospermia AZFc microdeletion: 23 No Y chromosome microdeletion (included other chromosomal abnormalities): 312 Male age in years, mean (SD): 31.5 (4.1) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	All participants had partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE The no Y chromosome microdeletion group included n=221 with idiopathic infertility (surgical sperm retrieval rate in this group:

Study	Population	Prognostic factor comparisons	Outcomes	Comments
				69/221), n=58 with KS, n=21 with undescended testes, and n=12 post-infectious disease
Goncalves 2017 Retrospective cohort study Portugal	N=65 Non-obstructive azoospermia AZFc microdeletion: 44 AZFb microdeletion: 13 AZFa microdeletion: 8 Male age in years; mean (SD): 33.8 (NR; range 24-50) Duration of infertility in years; mean (SD): 4.2 (NR; range 1-16)	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	Unclear whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: TESE (testicular biopsy)
Guneri 2016 Prospective cohort study Turkey	N=118 Non obstructive azoospermia AZFc microdeletion: 8 AZFb and c microdeletion: 1 AZFb microdeletion: 5 AZFa microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 103 Male age in years, mean (SD): NR Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: TESE
Hopps 2003	N=58	• AZFc microdeletion	• Sperm retrieval rate	The study did not specify

Study	Population	Prognostic factor comparisons	Outcomes	Comments
Retrospective cohort study USA	Azoospermia AZFc microdeletion: 32 AZFa, b and c microdeletion: 4 AZFb and c microdeletion: 10 AZFb microdeletion: 9 AZFa microdeletion: 3 Male age in years, mean (SD): NR Duration of infertility in years, mean (SD): NR	(isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	by surgical intervention: Sperm suitable for ICSI	whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: Micro-TESE (n=28) or biopsy (n=30)
Iijima 2020 Retrospective cohort study Japan	N=147 Non-obstructive azoospermia AZFc microdeletion: 10 AZFbc microdeletion: 1 No chromosomal abnormality: 136 Male age in years; mean (SD): 35.0 (6.3) Duration of infertility in years, mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis) • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Iwahata 2017	N=980	• Y chromosome microdeletion (any) versus no Y	• Sperm retrieval rate by surgical	Participants had complete

Study	Population	Prognostic factor comparisons	Outcomes	Comments
Prospective cohort study Japan	Non-obstructive azoospermia AZFc microdeletion: 43 AZFa, b and c microdeletion: 7 AZFb and c microdeletion: 20 AZFb microdeletion: 8 AZFa microdeletion: 1 No chromosomal abnormality: 901 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR	chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis) • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	intervention: NR if sperm suitable for ICSI	AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Johnson 2019 Retrospective cohort study UK	N=447 Non-obstructive azoospermia AZFc microdeletion: 21 AZFb microdeletion: 3 No chromosomal abnormality: 423 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis) • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE

Study	Population	Prognostic factor comparisons	Outcomes	Comments
		• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)		
Kihaile 2004 Prospective cohort study Japan	N=6 Non-obstructive azoospermia AZFc microdeletion: 2 AZFa, b and c microdeletion: 1 Beyond AZFc microdeletion (sY202, 243): 2 AZFa microdeletion: 1 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: Cryo-TESE
Kizilay 2019 Retrospective cohort study Turkey	N=67 Azoospermia AZFc microdeletion: 27 AZFb and c microdeletion: 13 AZFb microdeletion: 13 AZFa microdeletion: 14 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Kizilkan 2019 Retrospective cohort study Turkey	N=312 Non-obstructive azoospermia AZFc microdeletion: 16 No Y chromosome microdeletion	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion

Study	Population	Prognostic factor comparisons	Outcomes	Comments
	(included other chromosomal abnormalities): 296 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	no Y chromosome microdeletion		Surgical sperm retrieval method: micro-TESE The study included people with KS (n=81) but unclear if any of this group also had Y-chromosome microdeletions or were only included in the control arm
Klami 2018 Retrospective cohort study Finland	N=100 Non-obstructive azoospermia AZFc microdeletion: 7 No Y chromosome microdeletion (included other chromosomal abnormalities): 93 Male age in years; mean (SD): 33.4 (NR; range 21-47) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE The no Y chromosome microdeletion group included n=65 with idiopathic infertility (surgical sperm retrieval rate in this group: 20/65), n=15 with KS, n=10 with undescended testes, and n=3 post-gonadotoxic treatment
Ko 2016 Retrospective cohort study Hong Kong	N=70 Non-obstructive azoospermia AZFc microdeletion: 6 AZFa, b and c microdeletion: 1	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion

Study	Population	Prognostic factor comparisons	Outcomes	Comments
	AZFb and c microdeletion: 2 No chromosomal abnormality: 61 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis) • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)		Surgical sperm retrieval method: TESE Participants with AZFa, b and c, and those with AZFb and c microdeletions also had karyotypic abnormalities (n=3)
Ku 2017 Retrospective cohort study Taiwan	N=200 Non-obstructive azoospermia AZFc microdeletion: 31 AZFa or AZFb microdeletion: 3 No Y chromosome microdeletion (included other chromosomal abnormalities): 166 Male age in years; mean (SD): 35.1 (4.5) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis) • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	n=4 and n=27 had complete and partial AZFc microdeletion, respectively Surgical sperm retrieval method: micro-TESE The no Y chromosome microdeletion group included n=60 with idiopathic infertility (surgical sperm retrieval rate in this group: 13/60), n=24 with KS, n=11 with other chromosomal abnormalities, n=15 with undescended testes, n=3 post-infectious

Study	Population	Prognostic factor comparisons	Outcomes	Comments
		combination with other loci)		disease, n=4 post-gonadotoxic treatment, n=7 with hypogonadotrophic hypogonadism, and n=42 with varicoceles
Lan 2022 Retrospective cohort study China	N=968 Non-obstructive azoospermia AZFc microdeletion: 86 No Y chromosome microdeletion (included other chromosomal abnormalities): 882 Male age in years; mean (SD): 31.5 (4.8) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE For 391/432 (91%) sperm was suitable for ICSI The no Y chromosome microdeletion group included n=463 with idiopathic infertility (surgical sperm retrieval rate in this group: 144/463), n=241 with KS, n=109 with undescended testes, and n=69 with inflammation of testicle(s)
Lo Giacco 2014 Retrospective cohort study Spain	N=11 Azoospermia AZFc microdeletion: 10 AZFa microdeletion: 1	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	Participants had complete AZFc microdeletion Surgical sperm retrieval method: TESE

Study	Population	Prognostic factor comparisons	Outcomes	Comments
	Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR			
Mahdy 2024 Retrospective cohort study Italy	N=172 Non-obstructive azoospermia AZFc microdeletion: 5 AZFb microdeletion: 1 AZFa microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 165 Male age in years; mean (SD): 37.5 (6.4) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Mascarenhas 2016 Prospective cohort study India	N=9 Non-obstructive azoospermia AZFc microdeletion: 2 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 2 AZFb microdeletion: 4 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletions Surgical sperm retrieval method: TESA (n=8) or micro-TESE (n=1) Participants with AZFc (n=1 with KS), AZFa, b and c (n=1), and AZFb and c (n=1) microdeletions also had

Study	Population	Prognostic factor comparisons	Outcomes	Comments
				karyotypic abnormalities
Miraghazadeh 2019 Prospective cohort study Iran	N=200 Non-obstructive azoospermia AZFc microdeletion: 16 No chromosomal abnormality: 184 Male age in years; mean (SD): 39.2 (6.4) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	Participants had partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Park 2013 Retrospective cohort study Korea	N=58 Non-obstructive azoospermia AZFc microdeletion: 31 AZFb and c microdeletion: 14 AZFb microdeletion: 8 AZFa microdeletion: 5 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletions Surgical sperm retrieval method: multiple micro-TESE For all participants identified to have a Y chromosome microdeletion 2/168 had severe oligozoospermia but unclear if these participants included in the data analysed for this sample (n=58) where surgical sperm retrieval was attempted
Patrat 2010 Retrospective cohort study	N=27 Azoospermia	• AZFc microdeletion (isolated) versus AZFa or AZFb	• Sperm retrieval rate by surgical intervention:	The study did not specify whether participants

Study	Population	Prognostic factor comparisons	Outcomes	Comments
France	AZFc microdeletion: 18 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 2 AZFb microdeletion: 6 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	microdeletion (isolated or in combination with other loci)	Sperm suitable for ICSI	had complete or partial AZFc microdeletions Surgical sperm retrieval method: TESE (biopsy)
Schwarzer 2016 Retrospective cohort study Germany	N=25 Non-obstructive azoospermia AZFc microdeletion: 20 AZFb and c microdeletion: 2 AZFc and other chromosomic disorders: 2 AZFb microdeletion: 1 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletions Surgical sperm retrieval method: TESE (n=11) or micro-TESE (n=14)
Sen 2023 Retrospective cohort study Turkey	N=450 Non-obstructive azoospermia AZFc microdeletion: 12 AZFb microdeletion: 2 No chromosomal abnormality: 436 Male age in years; mean (SD): 33.3 (5.6) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE

Study	Population	Prognostic factor comparisons	Outcomes	Comments
		• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci) • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)		
Silber 1998 Retrospective cohort study USA	N=51 Non-obstructive azoospermia AZFc microdeletion: 10 No Y chromosome microdeletion (other chromosomal abnormalities NR): 41 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	n=5 and n=5 had complete and partial AZFc microdeletion, respectively Surgical sperm retrieval method: conventional TESE
Simoni 2008 Prospective cohort study Germany	N=16 Azoospermia or severe oligozoospermia (proportion NR) AZFc microdeletion: 10 AZFb + c microdeletion: 2 AZFb microdeletion: 2 AZFa microdeletion: 2 Male age in years; mean (SD): 32.1 (6.4)	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	Participants had partial AZFc microdeletion Surgical sperm retrieval method: TESE (bilateral testicular biopsy)

Study	Population	Prognostic factor comparisons	Outcomes	Comments
	Duration of infertility in years; mean (SD): NR			
Stahl 2010 & 2011 Retrospective cohort study USA	N=448 Non-obstructive azoospermia AZFc microdeletion: 43 AZFa, b and c microdeletion: 4 AZFb and c microdeletion: 7 AZFb microdeletion: 7 AZFa microdeletion: 2 No chromosomal abnormality: 385 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis) • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	n=21 and n=22 had complete and partial AZFc microdeletion, respectively Surgical sperm retrieval method: micro-TESE
Tian 2023 Retrospective cohort study China	N=1822 Non-obstructive azoospermia AZFc microdeletion: 108 No Y chromosome microdeletion (included other chromosomal abnormalities): 1714 Male age in years; mean (SD): 30.9 (5.2) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE The no Y chromosome microdeletion group included n=1154 with idiopathic infertility

Study	Population	Prognostic factor comparisons	Outcomes	Comments
				(surgical sperm retrieval rate in this group: 352/1154), n=297 with KS, n=158 with undescended testes, and n=105 post-infectious disease
Tsujimura 2004 Retrospective cohort study Japan	N=57 Non-obstructive azoospermia AZFc microdeletion: 1 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 54 Male age in years; mean (SD): 32.4 (4.6) Duration of infertility in years; mean (SD): 3.5 (2.6)	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The participant in the AZFc group had partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Uzay 2021 Retrospective cohort study Turkey	N=42 Azoospermia AZFc microdeletion: 31 AZFa, b and c microdeletion: 2 AZFb and c microdeletion: 4 AZFb microdeletion: 2 AZFa microdeletion: 3	• AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE

Study	Population	Prognostic factor comparisons	Outcomes	Comments
	Male age in years; mean (SD): 35.1 (7.1) Duration of infertility in years; mean (SD): NR			
Yamaguchi 2020 Retrospective cohort study Japan	N=584 Non-obstructive azoospermia AZFc microdeletion: 50 No Y chromosome microdeletion (other chromosomal abnormalities NR): 534 Male age in years; mean (SD): 34.1 (5.5) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion	• Sperm retrieval rate by surgical intervention: Sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE
Zeadna 2020 Retrospective cohort study Israel	N=119 Non-obstructive azoospermia AZFc microdeletion: 3 AZFa microdeletion: 1 No Y chromosome microdeletion (included other chromosomal abnormalities): 115 Male age in years; mean (SD): 33.0 (7.8) Duration of infertility in years; mean (SD): NR	• Y chromosome microdeletion (any) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)	• Sperm retrieval rate by surgical intervention: NR if sperm suitable for ICSI	The study did not specify whether participants had complete or partial AZFc microdeletion Surgical sperm retrieval method: conventional TESE The no Y chromosome microdeletion group included n=8 with KS
Zhang 2021	N=769 Non-obstructive azoospermia	• Y chromosome microdeletion (any) versus no Y	• Sperm retrieval rate by surgical intervention:	The study did not specify whether participants

Study	Population	Prognostic factor comparisons	Outcomes	Comments
Retrospective cohort study China	AZFc microdeletion: 91 No Y chromosome microdeletion (included other chromosomal abnormalities): 678 Male age in years; mean (SD): 30.1 (4.7) Duration of infertility in years; mean (SD): NR	chromosome microdeletion • AZFc microdeletion (isolated) versus no Y chromosome microdeletion • AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)	Sperm suitable for ICSI	had complete or partial AZFc microdeletion Surgical sperm retrieval method: micro-TESE The no Y chromosome microdeletion group included n=319 with idiopathic infertility (surgical sperm retrieval rate in this group: 98/319), n=284 with KS, n=52 with undescended testes, and n=23 post-infectious disease

AZF: azoospermia factor; ICSI: intracytoplasmic sperm injection; IQR: interquartile range; KS: Klinefelter syndrome; micro-TESE: microdissection testicular sperm extraction; NR: not reported; SD: standard deviation; SSR: surgical sperm retrieval; TESA: testicular sperm aspiration; TESE: testicular sperm extraction

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Y chromosome microdeletion (any) versus no Y chromosome microdeletion

Very low quality evidence from 28 studies showed no clinically important difference in surgical sperm retrieval rate between people with Y chromosome microdeletion (any) and those without Y chromosome microdeletion.

AZFc microdeletion (isolated) versus no Y chromosome microdeletion

Very low quality evidence from 26 studies showed a higher surgical sperm retrieval rate for participants with an isolated AZFc microdeletion relative to those with no Y chromosome microdeletion.

AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)

Very low quality evidence from 16 studies showed a higher surgical sperm retrieval rate for people with an isolated AZFc microdeletion relative to those with no chromosomal abnormality.

AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion

Very low quality evidence from 15 studies showed a lower surgical sperm retrieval rate for people with AZFa or AZFb microdeletions either as isolated microdeletions or in combination with other loci relative to those with no Y chromosome microdeletion.

AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)

Very low quality evidence from 26 studies showed a higher surgical sperm retrieval rate for people with an isolated AZFc microdeletion relative to those who had AZFa or AZFb microdeletions either as isolated microdeletions or in combination with other loci.

In this review, we planned to subgroup the evidence by age, and by complete and partial AZFc microdeletion. However, subgroup analysis could not be conducted because the majority of studies did not report age or type of AZFc microdeletion.

See appendix F for full GRADE tables.

Economic evidence

This evidence review is a prognostic review question and therefore, no health economic searches were conducted as economic evidence was not deemed relevant.

Included studies

As no health economic search was conducted for this review question, no health economic studies were included.

Excluded studies

No health economic studies were excluded for this review question as no health economic search was conducted.

Economic model

Economic modelling was not undertaking as this was a prognostic review and therefore did not involve a comparison of competing alternatives.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Surgical sperm retrieval (SSR) rate was prioritised as the only outcome by the committee. The committee considered this a critical outcome in order to effectively counsel men with non-obstructive azoospermia or severe oligozoospermia about the likelihood that sperm suitable for ICSI will be retrieved, and to inform recommendations about whether Y chromosome microdeletion testing should be offered.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The quality of evidence was very low. The main reasons for downgrading were risk of bias (because of limited information regarding baseline characteristics of the study population, study attrition, limited information about outcome and prognostic factor measurements, and failure to control

for potential confounders), inconsistency (serious heterogeneity unexplained by subgroup analysis) and imprecision (95% confidence intervals crossing decision making thresholds).

Benefits and harms

The committee discussed the evidence that appeared to show a higher surgical sperm retrieval rate in people with Y chromosome AZFc microdeletion relative to those with no Y chromosome microdeletion or no chromosomal abnormality and interpreted this finding as arising because of inherent bias in the selection of the control group in these studies. The committee highlighted that because the control groups are those undergoing surgical sperm retrieval, they may include people with more severe forms of testicular dysfunction, spermatogenic arrest or hypo-spermatogenesis, such as Sertoli cell-only syndrome and Klinefelter syndrome, and this may account for the counter-intuitive finding. The committee agreed that this evidence should be interpreted as showing that surgical sperm retrieval is non-inferior in the context of a Y chromosome AZFc microdeletion rather than this abnormality conferring an advantage. Based on this evidence and their clinical knowledge and experience, the committee did not consider it appropriate to include a recommendation for people with Y chromosome AZFc microdeletion. They agreed that a positive recommendation was not consistent with their interpretation of the evidence showing equivalence, but the evidence also did not show lower success for this group, and current NHS practice was appropriate.

The committee discussed the evidence showing a lower surgical sperm retrieval rate in people with Y chromosome AZFa or AZFb microdeletion (isolated or in combination with other loci) relative to people with Y chromosome AZFc microdeletion or those with no Y chromosome microdeletion. The committee highlighted the results of Goncalves 2017 as an outlier and agreed that the surgical sperm retrieval rate of 38% for those with an AZFa or b microdeletion is implausibly high. The committee questioned whether this was mature sperm and noted that the study did not report whether the microdeletions were complete or partial. However, with the exception of this study, the evidence aligned with the committee's knowledge and experience that the chances of successful surgical sperm retrieval for people with Y chromosome AZFa and AZFb microdeletions is almost non-existent. To avoid unnecessary surgical sperm retrieval with no chance of success, the committee recommended that testing for Y chromosome microdeletion should be performed as routine clinical practice to investigate idiopathic azoospermia. The committee was aware of a systematic review of 37 European and North American studies (N=12492 oligozoospermic men), which showed that the majority of Y chromosome microdeletions occur in those with sperm concentrations less than or equal to 1 million per ml, while fewer than 1% are identified in those with sperm concentrations greater than 1 million per ml (Kohn 2019). The committee therefore restricted this recommendation to those with idiopathic azoospermia or a sperm concentration of less than 1 million per ml as in clinical practice testing for Y chromosome microdeletion would not be offered to people with known causes of azoospermia and testing those with higher sperm concentrations (>1 million per ml) might not be cost effective. Based on their clinical knowledge and experience and the evidence reviewed the committee recommended that surgical sperm retrieval should not be offered to people with Y chromosome AZFa or AZFb microdeletion.

Cost effectiveness and resource use

No health economic search was conducted for this review question as it was a prognostic review.

The committee restricted the recommendation to individuals with idiopathic azoospermia or a sperm concentration of less than 1 million per ml. They believed this change would help avoid ineffective surgical sperm retrievals and reduce the number of tests performed, since testing is currently offered to people with sperm counts of up to 5 million per ml. Therefore,

the committee concluded that testing for microdeletion prior to surgical sperm retrieval is likely to be a cost-effective use of NHS resources.

Although the recommendations made for this review question are a change in current NHS practice, the committee concluded it was unlikely the recommendations made will result in a significant resource impact – noting there was even a possibility they could be cost saving.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.17.7 and 1.26.1.

References – included studies

Prognostic

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42023467982
Review title	Predictive value of Y chromosome microdeletions (positive AZF a, b, and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia
Review question	What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?
Objective	To determine the predictive value of positive AZF a, b, and c for sperm retrieval, to inform recommendations about whether Y chromosome microdeletion testing should be offered to people with non-obstructive azoospermia or severe oligozoospermia
Searches	The following databases will be searched (with no date restriction): Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be restricted by: • English language

Field	Content
	• Human studies The guideline committee will decide whether and when to re-run the searches to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Investigations for male factor fertility problems
Population	Inclusion: • People with fertility problems associated with non-obstructive azoospermia or severe oligozoospermia Exclusion: • Management of recurrent miscarriage

Prognostic factors	• Y chromosome microdeletion testing for azoospermia factors (AZF) microdeletion
	  ○ AZFa
	  ○ AZFb
	  ○ AZFc

Comparator	• Head-to-head comparison between AZFa, AZFb, and AZFc • No Y chromosome microdeletion
Types of study to be included	• Systematic reviews of cohort studies • Prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies
Other exclusion criteria	Other exclusion criteria: • Language limitations: studies published not in English-language (unless data can be obtained, and risk of bias assessed, from an existing systematic review) • Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted (and risk of bias assessed) from elsewhere (for instance, from an existing systematic review)

Field	Content
Context	This guidance will fully update the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
Primary outcomes (critical outcomes)	• Sperm retrieval rate by surgical intervention (as defined by study, risk of bias assessments will reflect where this is not defined as sperm suitable for ICSI)
Secondary outcomes (important outcomes)	N/A
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies included after full-text review. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the Y chromosome microdeletions, details of any factors adjusted for, setting, time period or number of cycles over which the outcome was predicted (the unit of analysis), relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Quality in Prognostic Studies (QUIPS) tool for prognostic studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Where multiple studies report on the same prognostic factor and the definitions used and approach to analysis in the primary papers is sufficiently consistent, the evidence will be meta-analysed using Cochrane Review Manager software. Random effects meta-analyses will be conducted (to allow for unexplained heterogeneity across prognosis studies) and data will be presented as risk ratios if possible or odds ratios when required

Field	Content	
	(for example, if only an adjusted odds ratio is reported). Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/". • An association between prognostic factor and outcome will be considered clinically important where RR/OR <0.80 and >1.25.	
Analysis of sub-groups	Evidence will be subgrouped by: • Complete and partial AZFc • AZFc complete • AZFc partial Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Male age (based on the mean age in the study): ○ <45 years ○ ≥45 years Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☐	Intervention
	☐	Diagnostic
	☒	Prognostic

Field	Content			
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify) Proportional (single-arm) meta-analysis		
Language	English			
Country	England			
Anticipated or actual start date	August 2023			
Anticipated completion date	November 2024			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	Named contact: Guideline Development Team A Named contact e-mail: FertilityProblems@nice.org.uk Organisational affiliation of the review: Guideline Development Team A, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)			
Review team members	• Senior Technical Analyst • Technical Analyst			
Funding sources/sponsor	This systematic review is being completed by NICE.			

Field	Content	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263	
Other registration details	None	
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023467982	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Y microdeletions, AZF, azoospermia factors, sperm retrieval, male infertility	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published

Field	Content	
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

AZF: azoospermia factor; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; ICSI: intracytoplasmic sperm injection; N/A: not applicable; NICE: National Institute for Health and Care Excellence; QUIPS: Quality in Prognostic Studies; ROBIS: risk of bias in systematic reviews

Appendix B Literature search strategies

Literature search strategies for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

Database: Ovid MEDLINE(R) ALL 1946 to June 04, 2024

Date of last search: 05/06/2024

#	Searches
1	exp infertility, male/
2	(male/ or men/ or exp "Sexual and Gender Minorities"/) and (Infertility/ or fertility/)
3	((male? or men or man or transgender* or trans gender* or transwom?n or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter sex* or nonbinary or non binary or TGNB or genderqueer* or two spirit or sex reassign* or "assigned male at birth" or AMAB or agender) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
4	((trans or transgender*) adj1 (wom?n or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
5	(gender adj1 (expansive* or queer* or nonconform* or "non conform*" or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
6	Azoospermia/ or Oligospermia/
7	(azoosperm* or NOA).tw,kf.
8	(cryptosperm* or cryptozoosperm* or hyposperm* or oligoasthenosperm* or oligoasthenoteratozoosperm* or oligoasthenozoosperm* or oligosperm* or oligozoosperm*).tw,kf.
9	((absence or absent or decreas* or fail* or inabilit* or insufficien* or lack* or low* or no or reduc* or suboptimal* or unable) adj3 sperm*).tw,kf.
10	or/1-9
11	Cytogenetic Analysis/ or Cytogenetics/ or Genetic Markers/ or Genetic Predisposition to Disease/ or Genetic Testing/ or Genetics/ or exp Karyotyping/ or "Predictive Value of Tests"/ or ge.fs.
12	exp Y Chromosome/
13	11 and 12
14	Chromosome Deletion/ or Deleted in Azoospermia 1 Protein/
15	karyotyp*.tw,kf.
16	(azoosperm* factor* or (Y adj3 chromosom*) or Yq or Yq11).tw,kf.
17	(partial* adj2 (delet* or microdelet* or monosom*)).tw,kf.
18	(AZF or AZFa or AZFb or AZFc or AZFb+c or AZF1 or AZF2 or DAZ*1 or "b1/b3" or "b2/b3" or "b2/b4" or "gr/gr" or TTY2* or YCM*1 or YCMD*1).tw,kf.
19	or/13-18
20	10 and 19
21	letter/
22	editorial/
23	news/
24	exp historical article/
25	Anecdotes as topic/
26	comment/
27	case reports/
28	(letter or comment*).ti.
29	animals/ not humans/

#	Searches
30	exp Animals, Laboratory/
31	exp Animal Experimentation/
32	exp Models, Animal/
33	exp Rodentia/
34	(rat or rats or rodent* or mouse or mice).ti.
35	or/21-34
36	20 not 35
37	limit 36 to english language

Database: Embase 1974 to 2024 June 04

Date of last search: 05/06/2024

#	Searches
1	exp male infertility/ or semen abnormality/
2	(male/ or "sexual and gender minority"/ or "transgender and gender nonbinary"/) and (infertility/ or subfertility/)
3	((male? or men or man or transgender* or trans gender* or transwom?n or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter sex* or nonbinary or non binary or TGNB or genderqueer* or two spirit or sex reassign* or "assigned male at birth" or AMAB or agender) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
4	((trans or transgender*) adj1 (wom?n or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
5	(gender adj1 (expansive* or queer* or nonconform* or "non conform*" or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) adj4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)).tw.
6	(azoosperm* or NOA).tw,kf.
7	(cryptosperm* or cryptozoosperm* or hyposperm* or oligoasthenosperm* or oligoasthenoteratozoosperm* or oligoasthenozoosperm* or oligosperm* or oligozoosperm*).tw,kf.
8	((absence or absent or decreas* or fail* or inabilit* or insufficien* or lack* or low* or no or reduc* or suboptimal* or unable) adj3 sperm*).tw,kf.
9	or/1-8
10	chromosome analysis/ or cytogenetic analysis/ or cytogenetics/ or genetic predisposition/ or genetic marker/ or genetic screening/ or genetics/ or karyotype/ or exp karyotyping/ or karyotyping system/ or marker chromosome/ or predictive value/ or prognostic assessment/
11	Y chromosome/
12	10 and 11
13	chromosome deletion Y/ or deleted in azoospermia protein 1/
14	karyotyp*.tw,kf.
15	((azoosperm* factor* or chromosom* or Y or Yq or Yq11) adj5 (delet* or microdelet* or subdelet*)).tw,kf.
16	(partial* adj2 (delet* or microdelet* or monosom*)).tw,kf.
17	(AZF or AZFa or AZFb or AZFc or AZFb+c or AZF1 or AZF2 or DAZ*1 or "b1/b3" or "b2/b3" or "b2/b4" or "gr/gr" or TTY2* or YCM*1 or YCMD*1).tw,kf.
18	or/12-17
19	9 and 18
20	letter.pt. or letter/
21	note.pt.
22	editorial.pt.
23	case report/ or case study/
24	(letter or comment*).ti.
25	animal/ not human/
26	nonhuman/
27	exp Animal Experiment/
28	exp Experimental Animal/
29	animal model/
30	exp Rodent/

#	Searches
31	(rat or rats or rodent* or mouse or mice).ti.
32	or/20-31
33	19 not 32
34	limit 33 to english language
35	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
36	34 not 35

Database: Cochrane Database of Systematic Reviews, Issue 6 of 12, June 2024

Date of last search: 05/06/2024

#	Searches
1	MeSH descriptor: [Male] explode all trees
2	MeSH descriptor: [Men] this term only
3	MeSH descriptor: [Sexual and Gender Minorities] explode all trees
4	{or #1-#3}
5	MeSH descriptor: [Infertility] this term only
6	MeSH descriptor: [Fertility] this term only
7	{or #5-#6}
8	#4 and #7
9	MeSH descriptor: [Infertility, Male] explode all trees
10	((male* or men or man or transgender* or trans next gender* or transwomen or transwoman or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter next sex* or nonbinary or "non binary" or TGNB or genderqueer* or "two spirit" or sex next reassign* or "assigned male at birth" or AMAB or agender) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
11	((trans or transgender*) near/1 (woman or women or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
12	(gender near/1 (expansive* or queer* or nonconform* or non next conform* or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
13	MeSH descriptor: [Azoospermia] this term only
14	MeSH descriptor: [Oligospermia] this term only
15	(azoosperm* or NOA):ti,ab,kw
16	(cryptosperm* or cryptozoosperm* or hyposperm* or oligoasthenosperm* or oligoasthenoteratozoosperm* or oligoasthenozoosperm* or oligosperm* or oligozoosperm*):ti,ab,kw
17	((absence or absent or decreas* or fail* or inabilit* or insufficien* or lack* or low* or no or reduc* or suboptimal* or unable) near/3 sperm*):ti,ab,kw
18	{or #8-#17}
19	MeSH descriptor: [Cytogenetic Analysis] this term only
20	MeSH descriptor: [Cytogenetics] this term only
21	MeSH descriptor: [Genetic Markers] this term only
22	MeSH descriptor: [Genetic Predisposition to Disease] this term only
23	MeSH descriptor: [Genetic Testing] this term only
24	MeSH descriptor: [Genetics] this term only
25	MeSH descriptor: [Karyotyping] explode all trees
26	MeSH descriptor: [Predictive Value of Tests] this term only
27	MeSH descriptor: [] explode all trees and with qualifier(s): [genetics - GE]
28	{or #19-#27}
29	MeSH descriptor: [Y Chromosome] explode all trees
30	#29 and #28
31	MeSH descriptor: [Chromosome Deletion] this term only
32	MeSH descriptor: [Deleted in Azoospermia 1 Protein] this term only
33	karyotyp*:ti,ab,kw

#	Searches
34	(azoosperm* next factor* or Y near/3 chromosom* or Yq or Yq11):ti,ab,kw
35	(partial* near/2 (delet* or microdelet* or monosom*)):ti,ab,kw
36	(AZF or AZFa or AZFb or AZFc or "AZFb+c" or AZF1 or AZF2 or DAZ* or "b1/b3" or "b2/b3" or "b2/b4" or "gr/gr" or TTY2* or YCM*):ti,ab,kw
37	{or #30-#36}
38	#18 and #37 in Cochrane Reviews, Cochrane Protocols

Database: Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2024

Date of last search: 05/06/2024

#	Searches
1	MeSH descriptor: [Male] explode all trees
2	MeSH descriptor: [Men] this term only
3	MeSH descriptor: [Sexual and Gender Minorities] explode all trees
4	{or #1-#3}
5	MeSH descriptor: [Infertility] this term only
6	MeSH descriptor: [Fertility] this term only
7	{or #5-#6}
8	#4 and #7
9	MeSH descriptor: [Infertility, Male] explode all trees
10	((male* or men or man or transgender* or trans next gender* or transwomen or transwoman or transfemale* or transfeminine or transperson* or transpeople or transsex* or intersex* or inter next sex* or nonbinary or "non binary" or TGNB or genderqueer* or "two spirit" or sex next reassign* or "assigned male at birth" or AMAB or agender) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
11	((trans or transgender*) near/1 (woman or women or female* or feminin* or person* or people or sex* or patient* or identit* or nonbinary or "non binary") near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
12	(gender near/1 (expansive* or queer* or nonconform* or non next conform* or dysphori* or fluid* or divers* or neutral or reassign* or affirm* or variance* or Incongruent or minorit* or transition*) near/4 (infertil* or subfertil* or fertil* or hypofertil* or subfecund* or fecund* or infecund* or steril*)):ti,ab
13	MeSH descriptor: [Azoospermia] this term only
14	MeSH descriptor: [Oligospermia] this term only
15	(azoosperm* or NOA):ti,ab,kw
16	(cryptosperm* or cryptozoosperm* or hyposperm* or oligoasthenosperm* or oligoasthenoteratozoosperm* or oligoasthenozoosperm* or oligosperm* or oligozoosperm*):ti,ab,kw
17	((absence or absent or decreas* or fail* or inabilit* or insufficien* or lack* or low* or no or reduc* or suboptimal* or unable) near/3 sperm*):ti,ab,kw
18	{or #8-#17}
19	MeSH descriptor: [Cytogenetic Analysis] this term only
20	MeSH descriptor: [Cytogenetics] this term only
21	MeSH descriptor: [Genetic Markers] this term only
22	MeSH descriptor: [Genetic Predisposition to Disease] this term only
23	MeSH descriptor: [Genetic Testing] this term only
24	MeSH descriptor: [Genetics] this term only
25	MeSH descriptor: [Karyotyping] explode all trees
26	MeSH descriptor: [Predictive Value of Tests] this term only
27	MeSH descriptor: [] explode all trees and with qualifier(s): [genetics - GE]
28	{or #19-#27}
29	MeSH descriptor: [Y Chromosome] explode all trees
30	#29 and #28
31	MeSH descriptor: [Chromosome Deletion] this term only
32	MeSH descriptor: [Deleted in Azoospermia 1 Protein] this term only
33	karyotyp*:ti,ab,kw

#	Searches
34	(azoosperm* next factor* or Y near/3 chromosom* or Yq or Yq11):ti,ab,kw
35	(partial* near/2 (delet* or microdelet* or monosom*)):ti,ab,kw
36	(AZF or AZFa or AZFb or AZFc or "AZFb+c" or AZF1 or AZF2 or DAZ* or "b1/b3" or "b2/b3" or "b2/b4" or "gr/gr" or TTY2* or YCM*):ti,ab,kw
37	{or #30-#36}
38	#18 and #37
39	conference:pt or (clinicaltrials or trialsearch):so
40	#38 not #39 in Trials

Database: Epistemonikos

Date of last search: 05/06/2024

#	Searches
1	(((male* OR men OR man OR transgender* OR "trans gender" OR "trans genders" OR "trans gendered" OR transwoman OR transwomen OR transfemale* OR transfeminine OR transperson* OR transpeople OR transex* OR intersex* OR "inter sex" OR "inter sexual" OR nonbinary OR "non binary" OR TGNB OR genderqueer* OR "two spirit" OR "sex reassign" OR "sex reassigned" OR "sex reassignment" OR "sex reassignments" OR "assigned male at birth" or AMAB or agender) OR ((trans OR transgender*) AND (woman OR women OR female* OR feminin* OR person* OR people OR sex* OR patient* OR identit* OR nonbinary OR "non binary")) OR (gender AND (expansive* or queer* or nonconform* or "non conform" OR "non conforming" OR "non conformity" OR dysphori* OR fluid* OR divers* OR neutral OR reassign* OR affirm* OR variance* OR Incongruent OR minorit* OR transition*))) AND ((infertil* OR subfertil* OR fertil* OR subfecund* OR "sub fecundity" OR infecund* OR steril*) OR ((absence OR absent OR decreas* OR fail* OR inabilit* OR insufficien* OR lack* OR low* OR no OR reduc* OR suboptimal* OR sub-optimal* OR "sub optimal" OR "sub optimally" OR unable) AND sperm*) OR cryptosperm* OR cryptozoosperm* OR hyposperm* OR oligoasthenosperm* OR oligoasthenoteratozoosperm* OR oligoasthenozoosperm* OR oligosperm* OR oligozoosperm*))
2	((azoosperm* AND factor*) OR karyotop* OR “Y chromosome” OR “Y chromosomes” or “Y chromosomal” OR Yq OR Yq11 OR (partial* AND (delet* OR microdelet* OR monosom*)) OR AZF OR AZFa OR AZFb OR AZFc OR "AZFb+c" OR AZF1 OR AZF2 OR DAZ* OR "b1/b3" OR "b2/b3" OR "b2/b4" OR "gr/gr" OR TTY2* OR YCM*)
3	#1 AND #2

Health economic literature search strategies:

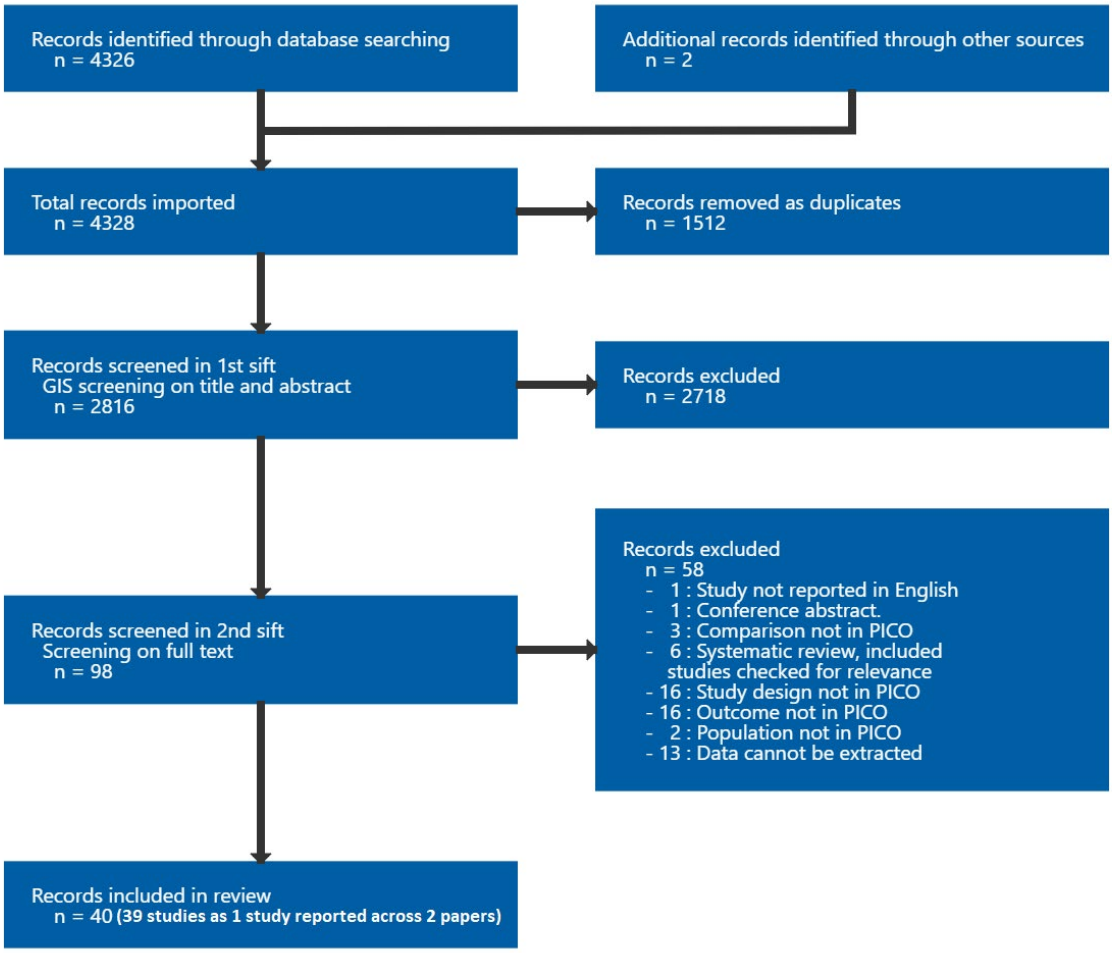
This was a qualitative/prognostic review question, therefore economic evidence was not relevant and thus no economic evidence searches were conducted.

Appendix C Prognostic evidence study selection

Study selection for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

Clinical search

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

Table 4: Evidence tables

Abur, 2019

Bibliographic Reference	Abur, Ummet; Gunes, Sezgin; Asci, Ramazan; Altundag, Engin; Akar, Omer S; Ayas, Bulent; Karadag Alpaslan, Mediniye; Ogur, Gonul; Chromosomal and Y-chromosome microdeletion analysis in 1,300 infertile males and the fertility outcome of patients with AZFc microdeletions.; Andrologia; 2019; vol. 51 (no. 11); e13402

Study details

Country/ies where study was carried out	Turkey
Study type	Prospective cohort study
Study dates	December 2004 - July 2017
Inclusion criteria	Infertile male with non-obstructive azoospermia or severe oligozoospermia (<5 x 10^6 spermatozoa/ml)
Exclusion criteria	Presence of endocrine disorders (predescribed androgen usage, hypophysectomy, hyperprolactinoma, and thyroid abnormalities), obstructive azoospermia (previous vasectomy, epididymitis, trauma, congenital bilateral agenesis of vas deferens, prostatectomy, bladder neck surgeries), orchidectomy, secondary infertility, radiation exposure, heat and/or prescribed use of drug, and testicular malignancy
Patient characteristics	N=94 Non-obstructive azoospermia AZFc microdeletion: 15

	No chromosomal abnormality: 79 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Urology clinic
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus No Y chromosome microdeletion

Outcome	**AZFc microdeletion, N = 15**	**No Y chromosome microdeletion, N = 79**
Sperm retrieval rate by surgical interventions (micro-TESE) No of events	n = 8	n = 52

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(About 36% of participants with AZFc microdeletion were lost to follow up)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description and measurement of the prognostic factor reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

AZF: azoospermia factor; ICSI: intracytoplasmic sperm injection

Arafa, 2018

Bibliographic Reference	Arafa, Mohamed M; Majzoub, Ahmad; AlSaid, Sami S; El Ansari, Walid; Al Ansari, Abdulla; Elbardisi, Yara; Elbardisi, Haitham T; Chromosomal abnormalities in infertile men with azoospermia and severe oligozoospermia in Qatar and their association with sperm retrieval intracytoplasmic sperm injection outcomes.; Arab journal of urology; 2018; vol. 16 (no. 1); 132-139

Study details

Country/ies where study was carried out	Qatar
Study type	Retrospective cohort study
Study dates	January 2008 - January 2012
Inclusion criteria	Male infertile patients with azoospermia or severe oligozoopspermia (<5 x 10^6 sperm/ml) who had karyotyping and Y chromosome microdeletion assay results
Exclusion criteria	NR
Patient characteristics	N=225 Azoospermia or severe oligozoospermia (proportion NR) AZFc microdeletion: 3 AZFb and c microdeletion: 2 No Y chromosome microdeletion (included other chromosomal abnormalities): 220 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFb and c microdeletion

	Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Tertiary hospital
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Testicular sperm extraction was done. The no Y chromosome microdeletion group included n=191 with idiopathic infertility (surgical sperm retrieval rate in this group: 111/191) and n=29 with chromosomal abnormalities other than Y chromosome microdeletions (including n=19 with KS)

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFb and c microdeletion versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 7	AZFb and c microdeletion, N = 5	Y chromosome microdeletion, N = 13	No Y chromosome microdeletion, N = 498
Sperm retrieval rate by surgical intervention (testicular sperm retrieval rate)	2/3	0/2	2/5	123/220

Outcome	AZFc microdeletion, N = 7	AZFb and c microdeletion, N = 5	Y chromosome microdeletion, N = 13	No Y chromosome microdeletion, N = 498
No of events				

AZF: azoospermia factor

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data reported for all participants who had surgical interventions)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement of outcome and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Brandell, 1998

Bibliographic Reference	Brandell, R A; Mielnik, A; Liotta, D; Ye, Z; Veeck, L L; Palermo, G D; Schlegel, P N; AZFb deletions predict the absence of spermatozoa with testicular sperm extraction: preliminary report of a prognostic genetic test.; Human reproduction (Oxford, England); 1998; vol. 13 (no. 1o); 2812-5

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	NR
Inclusion criteria	Patients with male factor infertility with non-obstructive azoospermia and severe oligozoospermia (<10 x 10^6 spermatozoa/ml)
Exclusion criteria	NR
Patient characteristics	N=80 Azoospermia AZFc microdeletion: 2 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 3

	AZFb microdeletion: 3 No Y chromosome microdeletion (other chromosomal abnormalities NR): 71 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Medical centre
Sources of funding	Not industry funded - The study was supported by the Edwin Beer Program of the New York Academy of Medicine
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 2	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 7	Y chromosome microdeletion, N = 9	No Y chromosome microdeletion, N = 71
Sperm retrieval rate by surgical intervention (TESE) No of events	n = 2	n = 0	n = 2	n = 45

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Cetinkaya, 2015

Bibliographic Reference	Cetinkaya, Mehmet; Onem, Kadir; Zorba, Orhan Unal; Ozkara, Hamdi; Alici, Bulent; Evaluation of Microdissection Testicular Sperm Extraction Results in Patients with Non-Obstructive Azoospermia: Independent Predictive Factors and Best Cutoff Values for Sperm Retrieval.; Urology journal; 2015; vol. 12 (no. 6); 2436-43

Study details

Country/ies where study was carried out	Turkey
Study type	Retrospective cohort study
Study dates	December 2006 - December 2009
Inclusion criteria	Patients with non-obstructive azoospermia with FSH, LH, testicular volume, free testosterone, total testosterone, inhibin B, Y chromosome microdeletion, and karyotype analysis results
Exclusion criteria	Non-palpable vas deference and obstructive azoospermia

Patient characteristics	N=191 Non-obstructive azoospermia AZFc microdeletion: 5 AZFa, b and c microdeletion: 1 AZFa and c microdeletion: 1 AZFb and c microdeletion: 2 AZFb microdeletion: 1 No Y chromosome microdeletion (included other chromosomal abnormalities): 181 Male age in years, mean (SD): 34.4 (5.6) Duration of infertility in years; mean (SD): 7.8 (5.1)
Risk factor(s) of interest	Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study used multivariate analysis. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	NR
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used. Disaggregated outcome data (based on loci of Y chromosome microdeletion) was not reported

	The no Y chromosome microdeletion group included n=175 with normal karyotypes (disaggregated sperm retrieval rate in this group not reported) and n=6 with KS

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	Y chromosome microdeletion, N = 10	No Y chromosome microdeletion, N = 181
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 1	n = 103

micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Place of recruitment was unclear)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Definition of outcome was unclear (e.g., unclear whether sperm was suitable for ICSI))*

Section	Question	Answer
Study Confounding	Study Confounding Summary	Low risk of bias *(The study adjusted for potential confounders (multivariate analysis was used).)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Chen, 2019

Bibliographic Reference	Chen, Xiangfeng; Ma, Yi; Zou, Shasha; Wang, Siqi; Qiu, Jin; Xiao, Qian; Zhou, Liang; Ping, Ping; Comparison and outcomes of nonobstructive azoospermia patients with different etiology undergoing MicroTESE and ICSI treatments.; Translational andrology and urology; 2019; vol. 8 (no. 4); 366-373

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	January 2013 - December 2017
Inclusion criteria	Patients with non-obstructive azoospermia who underwent microdissection testicular sperm extraction

Exclusion criteria	Obstructive azoospermia, abnormal karyotyping such as 46,XX, chromosome translocation, and complete AZFa or AZFb microdeletion
Patient characteristics	N=595 Non-obstructive azoospermia AZFc microdeletion: 34 No Y chromosome microdeletion (included other chromosomal abnormalities): 561 Male age in years; mean (SD): 29.4 (6.2) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Hospital
Sources of funding	Not industry funded - The study was supported by the National Natural Science Foundation of China.
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction was used.

	The no Y chromosome microdeletion group included n=446 with idiopathic infertility (surgical sperm retrieval rate in this group: 119/446), n=66 with KS, n=33 with undescended testes, n=13 post-infectious disease, and n=3 post-gonadotoxic treatment

AZF: azoospermia factor; BMI: body mass index; KS: Klinefelter syndrome; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 34	No Y chromosome microdeletion, N = 561
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 17	n = 184

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI was reported))*

Section	Question	Answer
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Choi, 2004

Bibliographic Reference	Choi, Janet M; Chung, Pak; Veeck, Lucinda; Mielnik, Anna; Palermo, Gianpiero D; Schlegel, Peter N; AZF microdeletions of the Y chromosome and in vitro fertilization outcome.; Fertility and sterility; 2004; vol. 81 (no. 2); 337-41

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	March 1996 - March 2002
Inclusion criteria	Participants with Y chromosome microdeletion and those with normal Y chromosome, who had severe oligozoospermia or non-obstructive azoospermia and underwent testicular sperm extraction procedure for IVF

Exclusion criteria	NR
Patient characteristics	N=34 (36 cycles) Non-obstructive azoospermia AZFc microdeletion: 6 (7 cycles) AZFb and c microdeletion: 2 (complete) AZFb microdeletion: 2 (1 complete, 1 partial) AZFa microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 23 (24 cycles) Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb (isolated or in combination with other loci) Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Academic infertility centre
Sources of funding	NR

Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Testicular sperm extraction procedure was used. Surgical sperm retrieval rate denominator reported as ICSI cycles

AZF: azoospermia factor; BMI: body mass index; ICSI: intracytoplasmic sperm injection; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 6	AZFa or AZFb (isolated or in combination with other loci), N = 5	Y chromosome microdeletion, N = 11	No Y chromosome microdeletion, N = 23
Sperm retrieval rate by surgical intervention (retrieval rate per TESE attempt) No of events	6/7	1/5	7/12	15/24

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Choi, 2013

Bibliographic Reference	Choi, Don Kyung; Gong, In Hyuck; Hwang, Jin Ho; Oh, Jong Jin; Hong, Jae Yup; Detection of Y Chromosome Microdeletion is Valuable in the Treatment of Patients With Nonobstructive Azoospermia and Oligoasthenoteratozoospermia: Sperm Retrieval Rate and Birth Rate.; Korean journal of urology; 2013; vol. 54 (no. 2); 111-6

Study details

Country/ies where study was carried out	Korea

Study type	Retrospective cohort study
Study dates	March 2004 - June 2011
Inclusion criteria	Infertile male with non-obstructive azoospermia or severe oligoasthenoteratozoospermia
Exclusion criteria	Participants who did not undergo testicular sperm extraction procedure
Patient characteristics	N=112 Non-obstructive azoospermia AZFc microdeletion microdeletion: 21 AZFb and c microdeletion: 9 No Y chromosome microdeletion (other chromosomal abnormalities NR): 82 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFbc microdeletion Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR

Setting	Hospital
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Multiple testicular sperm extraction procedures were used (which include multiple-site biopsies or single large incision with multiple samplings).

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFbc microdeletion versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 21	AZFbc microdeletion, N = 9	Y chromosome microdeletion, N = 30	No Y chromosome microdeletion, N = 82
Sperm retrieval rate by surgical interventions (multiple-TESE) No of events	8	0	8	21

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(Some participants (unclear how many) with Y chromosome microdeletions were loss to follow up)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description and measurement (objective method) of the prognostic factor reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement of outcome were used and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Deng, 2023

Bibliographic Reference	Deng, Chen-Yao; Liu, De-Feng; Zhao, Lian-Ming; Lin, Hao-Cheng; Mao, Jia-Ming; Zhang, Zhe; Yang, Yu-Zhuo; Zhang, Hai-Tao; Hong, Kai; Xu, Hui-Yu; Jiang, Hui; Development of a predictive model for increasing sperm retrieval success by microdissection testicular sperm extraction in patients with nonobstructive azoospermia.; Asian journal of andrology; 2023

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	January 2021 - December 2021
Inclusion criteria	Male aged 22-45 years with non-obstructive azoospermia (based on two consecutive semen analyses), and fertile female partner
Exclusion criteria	Male with hypothalamic or pituitary defects, Kallmann syndrome, and medications which affect hormone levels (e.g., selective estrogen receptor modulators, gonadotropins, exogenous testosterone, or aromatase inhibitors)
Patient characteristics	N=200 Non-obstructive azoospermia Y chromosome microdeletion (loci NR): 21 No Y chromosome microdeletion (included other chromosomal abnormalities): 179 Male age in years; mean (SD): NR (median 31, IQR 29-33) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	Binary logistic regression was used and six predictors (e.g., cryptorchidism and idiopathic non-obstructive azoospermia) were included in analyses. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR

Setting	Hospital
Sources of funding	Not industry funded - The study was supported by Peking University Clinical Medicine Youth Special Fund.
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used. The no Y chromosome microdeletion group included n=128 with idiopathic infertility (surgical sperm retrieval rate in this group: 35/128), n=24 with KS, n=15 with undescended testes, n=10 post-infectious disease, and n=2 post-gonadotoxic treatment

AZF: azoospermia factor; BMI: body mass index; IQR: interquartile range; NR: not reported; SD: standard deviation

Outcomes

Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	Y chromosome microdeletion, N = 21	No Y chromosome microdeletion, N = 179
Sperm retrieval rate by surgical interventions (micro-TESE) No of events	n = 8	n = 59

micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Measurement of prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	Low risk of bias *(Binary logistic regression was used.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Gao, 2022

Bibliographic Reference	Gao, Songzhan; Yang, Xianfeng; Xiao, Xiaoshuai; Yin, Shujun; Guan, Yichun; Chen, Jianhuai; Chen, Yun; Outcomes and affecting factors for ICSI and microTESE treatments in nonobstructive azoospermia patients with different etiologies: A retrospective analysis.; Frontiers in endocrinology; 2022; vol. 13; 1006208

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	January 2017 - December 2021
Inclusion criteria	Male participants with non-obstructive azoospermia, normal ejaculate volume and PH, absence of ejaculated sperm in minimum three semen samples, no seminal tract obstruction, and available clinical data, such as medical history, assessments of hormone, physical examination, scrotal ultrasound, and genetic testing
Exclusion criteria	Serious physical and mental health conditions, serious female infertility factors (such as tubal factors, anovulation, polycystic ovary syndrome, ovarian failure, hormonal and immunological infertility, and endometriosis
Patient characteristics	N=335 Non-obstructive azoospermia AZFc microdeletion: 23 No Y chromosome microdeletion (included other chromosomal abnormalities): 312 Male age in years, mean (SD): 31.5 (4.1) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.

Duration of follow-up	NR
Setting	Hospital
Sources of funding	Not industry funded - The study was supported by the 2021 Henan Medical Science and Technology Research Plan Joint Co-construction Project.
Other information	Complete or partial AZFc microdeletion: All participants had partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction was used. The no Y chromosome microdeletion group included n=221 with idiopathic infertility (surgical sperm retrieval rate in this group: 69/221), n=58 with KS, n=21 with undescended testes, and n=12 post-infectious disease

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	**AZFc microdeletion, N = 23**	**No Y chromosome microdeletion, N = 312**
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 14	n = 123

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Goncalves, 2017

Bibliographic Reference	Goncalves, Carolina; Cunha, Mariana; Rocha, Eduardo; Fernandes, Susana; Silva, Joaquina; Ferraz, Luis; Oliveira, Cristiano; Barros, Alberto; Sousa, Mario; Y-chromosome microdeletions in nonobstructive azoospermia and severe oligozoospermia.; Asian journal of andrology; 2017; vol. 19 (no. 3); 338-345

Study details

Country/ies where study was carried out	Portugal
Study type	Retrospective cohort study
Study dates	1995 - 2014
Inclusion criteria	Participants with AZF microdeletion treated with ICSI, using fresh or frozen-thawed testicular sperm or ejaculated sperm
Exclusion criteria	NR
Patient characteristics	N=65 Non-obstructive azoospermia AZFc microdeletion: 44 AZFb microdeletion: 13 AZFa microdeletion: 8 Male age in years; mean (SD): 33.8 (NR; range 24-50) Duration of infertility in years; mean (SD): 4.2 (NR; range 1-16)
Risk factor(s) of interest	AZFc microdeletion AZFa and AZFb microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR

Setting	Fertility clinic
Sources of funding	Not industry funded - The study was supported by National Funds through FCT-foundation for Science and Technology
Other information	Complete or partial AZFc microdeletion: Unclear whether participants (who had surgical sperm retrieval procedure) had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Testicular sperm extraction (testicular biopsy) procedure was used.

AZF: azoospermia factor; BMI: body mass index; ICSI: intracytoplasmic sperm injection; micro-TESE: microdissection testicular sperm extraction

Outcomes

AZFc microdeletion versus AZFa and AZFb microdeletion

Outcome	**AZFc microdeletion, N = 44**	**AZFa and AZFb microdeletion, N = 21**
Sperm retrieval rate by surgical intervention (TESE) No of events	n = 32	n = 8

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Guneri, 2016

Bibliographic Reference	Guneri, Cagri; Alkibay, Turgut; Tunc, Lutfi; Effects of clinical, laboratuary and pathological features on successful sperm retrieval in non-obstructive azoospermia.; Turkish journal of urology; 2016; vol. 42 (no. 3); 168-77

Study details

Country/ies where study was carried out	Turkey
Study type	Prospective cohort study
Study dates	2002 - 2007

Inclusion criteria	Men with male factor infertility and non-obstructive azoospermia
Exclusion criteria	Presence of obstructive azoospermia (suggested by the presence of non-palpable vas deferenses, ejaculate volume of <2 ml, normal testicular volume, normal FSH, LH and T levels, transrectal ultrasonographic examinations, magnetic resonance imaging findings, cystic fibrosis gene mutation tests, and seminal fructose analysis)
Patient characteristics	N=118 Non obstructive azoospermia AZFc microdeletion: 8 AZFb and c microdeletion: 1 AZFb microdeletion: 5 AZFa microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 103 Male age in years, mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Urology clinic and in-vitro fertilisation unit

Sources of funding	None - The study did not receive financial support.
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; FSH: follicular stimulating hormone; LH: luteinising hormone; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 8	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 7	Y chromosome microdeletion, N = 15	No Y chromosome microdeletion, N = 103
Sperm retrieval rate by surgical intervention (TESE) No of events	n = 2	n = 1	n = 3	n = 46

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for about 91% of participants who underwent testicular sperm extraction procedure)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Hopps, 2003

Bibliographic Reference	Hopps, C V; Mielnik, A; Goldstein, M; Palermo, G D; Rosenwaks, Z; Schlegel, P N; Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb and AZFc regions.; Human reproduction (Oxford, England); 2003; vol. 18 (no. 8); 1660-5

Study details

Country/ies where study was carried out	USA

Study type	Retrospective cohort study
Study dates	NR
Inclusion criteria	Men with Y chromosome microdeletion who presented for evaluation of infertility
Exclusion criteria	Patients who did not have semen analysis, diagnostic biopsy, and testicular sperm extraction procedure
Patient characteristics	N=58 Azoospermia AZFc microdeletion: 32 AZFa, b and c microdeletion: 4 AZFb and c microdeletion: 10 AZFb microdeletion: 9 AZFa microdeletion: 3 Male age in years, mean (SD): NR Duration of infertility in years, mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci)
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	NR

Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure (n=28) or biopsy (n=30) were used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci)

Outcome	**AZFc microdeletion, N = 32**	**AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 26**
Sperm retrieval rate by surgical intervention (micro-TESE or testicular biopsy) No of events	n = 18	n = 0

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and recruitment period not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure and azoospermia)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Iijima, 2020

Bibliographic Reference	Iijima, Masashi; Shigehara, Kazuyoshi; Igarashi, Hideki; Kyono, Koichi; Suzuki, Yasuo; Tsuji, Yuji; Kobori, Yoshitomo; Kobayashi, Hideyuki; Mizokami, Atsushi; Y chromosome microdeletion screening using a new molecular diagnostic method in 1030 Japanese males with infertility.; Asian journal of andrology; 2020; vol. 22 (no. 4); 368-371

Study details

Country/ies where study was carried out	Japan
Study type	Retrospective cohort study

Study dates	April 2014 - December 2016
Inclusion criteria	Male with infertility who underwent Y chromosome microdeletion assessment
Exclusion criteria	Presence of ejaculatory dysfunction, hypogonadism, history of chemotherapy and radiation therapy
Patient characteristics	N=147 Non-obstructive azoospermia AZFc microdeletion: 10 AZFbc microdeletion: 1 No chromosomal abnormality: 136 Male age in years; mean (SD): 35.0 (6.3) Duration of infertility in years, mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFbc microdeletion Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Hospital
Sources of funding	NR

Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFbc microdeletion versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 10	AZFbc microdeletion, N = 1	Y chromosome microdeletion, N = 11	No Y chromosome microdeletion, N = 136
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 6	n = 0	n = 6	n = 39

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had non-obstructive azoospermia and surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Iwahata, 2017

Bibliographic Reference	Iwahata, T.; Kobori, Y.; Shimomura, Y.; Suzuki, K.; Shin, T.; Song, S.; Okada, H.; Spermatogenic dysfunction in azoospermic japanese men caused by Y chromosome microdeletions; Dokkyo Journal of Medical Sciences; 2017; vol. 44 (no. 2); 151-155

Study details

Country/ies where study was carried out	Japan
Study type	Prospective cohort study
Study dates	NR

Inclusion criteria	Patients aged 20-51 years with primary infertility and non-obstructive azoospermia
Exclusion criteria	Obstructive azoospermia, microdeletion associated with abnormal karyotypes (such as 46,XX, 47,XXY and balanced rearrangements, including inversions or reciprocal translocations)
Patient characteristics	N=980 Non-obstructive azoospermia AZFc microdeletion: 43 AZFa, b and c microdeletion: 7 AZFb and c microdeletion: 20 AZFb microdeletion: 8 AZFa microdeletion: 1 No chromosomal abnormality: 901 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Hospital

Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: Participants had complete AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 43	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 36	Y chromosome microdeletion, N = 79	No Y chromosome microdeletion, N = 901
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 28	n = 0	n = 28	n = 297

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and recruitment period not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Limitation information about analytical strategy.)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Johnson, 2019

Bibliographic Reference	Johnson, Mark; Raheem, Amr; De Luca, Francesco; Hallerstrom, Marcus; Zainal, Yasmeen; Poselay, Sameer; Mohammadi, Baharak; Moubasher, Amr; Johnson, Thomas Frederick; Muneer, Asif; Sangster, Philippa; Ralph, David J; An analysis of the frequency of Y-chromosome microdeletions and the determination of a threshold sperm concentration for genetic testing in infertile men.; BJU international; 2019; vol. 123 (no. 2); 367-372

Study details

Country/ies where study was carried out	UK

Study type	Retrospective cohort study
Study dates	July 2004 - December 2016
Inclusion criteria	Men aged over 18 with infertility for >1 year, genetic analysis, and two abnormal semen analyses
Exclusion criteria	NR
Patient characteristics	N=447 Non-obstructive azoospermia AZFc microdeletion: 21 AZFb microdeletion: 3 No chromosomal abnormality: 423 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFb microdeletion Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Tertiary centre

Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFb microdeletion versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 21	AZFb microdeletion, N = 3	Y chromosome microdeletion, N = 24	No Y chromosome microdeletion, N = 423
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 7	n = 0	n = 7	n = 212

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure and non-obstructive azoospermia)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Kihaile, 2004

Bibliographic Reference	Kihaile, Paul E; Kisanga, Ramzy E; Aoki, Kazuo; Kumasako, Yoko; Misumi, Junichi; Utsunomiya, Takafumi; Embryo outcome in Y-chromosome microdeleted infertile males after ICSI.; Molecular reproduction and development; 2004; vol. 68 (no. 2); 176-81

Study details

Country/ies where study was carried out	Japan
Study type	Prospective cohort study

Study dates	NR
Inclusion criteria	Men with infertility, non-obstructive azoospermia, oligoasthenoteratozoospermia (sperm concentration <5 x 10^6/ml), and Y chromosome microdeletion
Exclusion criteria	History of testicular injury
Patient characteristics	N=6 Non-obstructive azoospermia AZFc microdeletion: 2 AZFa, b and c microdeletion: 1 Beyond AZFc nicrodeletion (sY202, 243): 2 AZFa microdeletion: 1 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci)
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Hospital
Sources of funding	NR

Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Cryo-testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci)

Outcome	**AZFc microdeletion, N = 2**	**AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 4**
Sperm retrieval rate by surgical intervention (cryo-TESE) No of events	n = 2	n = 0

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and recruitment period not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure and Y chromosome microdeletion)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(No information on analytical strategy and model development strategy reported)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Kizilay, 2019

Bibliographic Reference	Kizilay, Fuat; Semerci, Bulent; Simsir, Adnan; Kalemci, Serdar; Altay, Baris; Analysis of factors affecting repeat microdissection testicular sperm extraction outcomes in infertile men.; Turkish journal of urology; 2019; vol. 45 (no. supp1); 1-s6

Study details

Country/ies where study was carried out	Turkey
Study type	Retrospective cohort study
Study dates	January 2016 - June 2018

Inclusion criteria	Infertile men who underwent microdissection testicular sperm extraction procedure
Exclusion criteria	NR
Patient characteristics	N=67 Azoospermia AZFc microdeletion: 27 AZFb and c microdeletion: 13 AZFb microdeletion: 13 AZFa microdeletion: 14 Male age in years; mean (SD): NR Duration of infertility in years, mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci)
Confounding factor(s) of interest	The study used multivariate logistic regression model (that includes different predictors such as the number of testicular sperm extraction procedures, testicular volume, karyotype, testis histopathology, preoperative FSH, and Y chromosome microdeletion). In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Urology department
Sources of funding	None
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

	We did not extract the data on participants with abnormal karyotypes (N=47) as they might not be representative of the broader population without Y chromosome microdeletion.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci)

Outcome	**AZFc microdeletion, N = 27**	**AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 40**
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 19	n = 1

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Measurement of prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*

Section	Question	Answer
Study Confounding	Study Confounding Summary	Low risk of bias *(Multivariate logistic regression was used)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Kizilkan, 2019

Bibliographic Reference	Kizilkan, Yalcin; Toksoz, Serdar; Turunc, Tahsin; Ozkardes, Hakan; Parameters predicting sperm retrieval rates during microscopic testicular sperm extraction in nonobstructive azoospermia.; Andrologia; 2019; vol. 51 (no. 11); e13441

Study details

Country/ies where study was carried out	Turkey
Study type	Retrospective cohort study
Study dates	2003 - 2014
Inclusion criteria	Patients with fertility issues and non-obstructive azoospermia
Exclusion criteria	AZFa and AZFb microdeletions were excluded

Patient characteristics	N=312 Non-obstructive azoospermia AZFc microdeletion: 16 No Y chromosome microdeletion (included other chromosomal abnormalities): 296 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	Multivariate logistic regression model (that includes different predictors such as previous testicular biopsy, history varicocelectomy, testicular volume and so on) was used. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Urology clinic
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection or microscopic testicular sperm extraction procedure was used. The study included people with KS (n=81) but unclear if any of this group also had Y-chromosome microdeletions or were only included in the control arm

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 16	No Y chromosome microdeletion, N = 296
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 4	n = 104

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Measurement of prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	Low risk of bias *(Multivariate logistic regression was used (that includes different predictors))*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Klami, 2018

Bibliographic Reference	Klami, Rauni; Mankonen, Harri; Perheentupa, Antti; Microdissection testicular sperm extraction in Finland - results of the first 100 patients.; Acta obstetricia et gynecologica Scandinavica; 2018; vol. 97 (no. 1); 53-58

Study details

Country/ies where study was carried out	Finland
Study type	Retrospective cohort study
Study dates	2008 - 2015
Inclusion criteria	Patients with non-obstructive azoospermia and previous negative testicular biopsies
Exclusion criteria	NR
Patient characteristics	N=100 Non-obstructive azoospermia AZFc microdeletion: 7 No Y chromosome microdeletion (included other chromosomal abnormalities): 93 Male age in years; mean (SD): 33.4 (NR; range 21-47) Duration of infertility in years; mean (SD): NR

Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR (The study stated that pregnancy outcomes were followed but total duration of follow up was unclear)
Setting	Hospital
Sources of funding	None
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used. The no Y chromosome microdeletion group included n=65 with idiopathic infertility (surgical sperm retrieval rate in this group: 20/65), n=15 with KS, n=10 with undescended testes, and n=3 post-gonadotoxic treatment

AZF: azoospermia factor; BMI: body mass index; KS: Klinefelter Syndrome; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 7	No Y chromosome microdeletion, N = 93
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 4	n = 37

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(The study stated that follow-up data was not entirely complete, but unclear how many participants were lost to follow up.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(The study stated that genetic analysis was done but clear information about prognostic factor measurement or method was not provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Ko, 2016

Bibliographic Reference	Ko, J Ky; Chai, J; Lee, V Cy; Li, R Hw; Lau, E; Ho, K L; Tam, P C; Yeung, W Sb; Ho, P C; Ng, E Hy; Sperm retrieval rate and pregnancy rate in infertile couples undergoing in-vitro fertilisation and testicular sperm extraction for non-obstructive azoospermia in Hong Kong.; Hong Kong medical journal = Xianggang yi xue za zhi; 2016; vol. 22 (no. 6); 556-62

Study details

Country/ies where study was carried out	Hong Kong
Study type	Retrospective cohort study
Study dates	January 2001 - December 2013
Inclusion criteria	Couples who underwent the first IVF cycle and testicular sperm extraction procedure for non-obstructive azoospermia
Exclusion criteria	Obstructive azoospermia, ejaculatory dysfunction, and non-motile sperms in the ejaculate
Patient characteristics	N=70 Non-obstructive azoospermia AZFc microdeletion: 6 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 2 No chromosomal abnormality: 61 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) Y chromosome microdeletion

	No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	Participants who had an ongoing pregnancy were followed up until 12 weeks of gestation
Setting	Tertiary care hospital
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Conventional or microdissection testicular sperm extraction procedures were used. Participants with AZFa, b and c, and those with AZFb and c microdeletions also had karyotypic abnormalities (n=3)

AZF: azoospermia factor; BMI: body mass index; IVF: invitro fertilisation; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 6	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 3	Y chromosome microdeletion, N = 9	No Y chromosome microdeletion, N = 61
Sperm retrieval rate by surgical intervention (conventional or micro-TESE) No of events	n = 3	n = 0	n = 3	n = 28

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure and genetic information)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Ku, 2017

Bibliographic Reference	Ku, M.-H.; Huang, I.-S.; Lin, A.T.; Chen, K.-K.; Huang, W.J.; The predictive value of parameters of clinical presentations for sperm yield in patients with nonobstructive azoospermia receiving microdissection testicular sperm extraction; Urological Science; 2017; vol. 28 (no. 4); 243-247

Study details

Country/ies where study was carried out	Taiwan
Study type	Retrospective cohort study
Study dates	October 2009 - December 2014
Inclusion criteria	Patients with non-obstructive azoospermia who had microdissection testicular sperm extraction procedure
Exclusion criteria	NR
Patient characteristics	N=200 Non-obstructive azoospermia AZFc microdeletion: 31 AZFa or AZFb microdeletion: 3 No Y chromosome microdeletion (included other chromosomal abnormalities): 166 Male age in years; mean (SD): 35.1 (4.5) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) Y chromosome microdeletion No Y chromosome microdeletion

Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Urology department
Sources of funding	None
Other information	Complete or partial AZFc microdeletion: n=4 and n=27 had complete and partial AZFc microdeletion, respectively. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used. The no Y chromosome microdeletion group included n=60 with idiopathic infertility (surgical sperm retrieval rate in this group: 13/60), n=24 with KS, n=11 with other chromosomal abnormalities, n=15 with undescended testes, n=3 post-infectious disease, n=4 post-gonadotoxic treatment, n=7 with hypogonadotrophic hypogonadism, and n=42 with varioceles

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 31	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 3	Y chromosome microdeletion, N = 34	No Y chromosome microdeletion, N = 166
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 9	n = 0	n = 9	n = 55

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(The study stated that genetic testing was done, but detailed information about measurement of prognostic factor or method not provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Lan, 2022

Bibliographic Reference	Lan, Yu; Zheng, Haiyan; Fu, Xin; Peng, Tianwen; Liao, Chen; Liu, Jianan; Liu, Min; An, Geng; Clinical Outcomes and Live Birth Rate Resulted From Microdissection Testicular Sperm Extraction With ICSI-IVF in Non-Obstructive Azoospermia: A Single-Center Cohort Study.; Frontiers in endocrinology; 2022; vol. 13; 893679

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	January 2015 - December 2019
Inclusion criteria	Men with non-obstructive azoospermia who underwent micro-TESE
Exclusion criteria	NR
Patient characteristics	N=968 Non-obstructive azoospermia AZFc microdeletion: 86 No Y chromosome microdeletion (included other chromosomal abnormalities): 882 Male age in years; mean (SD): 31.5 (4.8) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.

Duration of follow-up	NR
Setting	Hospital
Sources of funding	Funded by the National Key R&D Plan, the National Natural Science Foundation of China, the Guangdong Natural Science Foundation and the Guangzhou Health Science and Technology Project
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction was used. The no Y chromosome microdeletion group included n=463 with idiopathic infertility (surgical sperm retrieval rate in this group: 144/463), n=241 with KS, n=109 with undescended testes, and n=69 with inflammation of testicle(s)

AZF: azoospermia factor; BMI: body mass index; KS: Klinefelter Syndrome; micro-TESE: microdissection testicular sperm extraction; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus No Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 86	No Y chromosome microdeletion, N = 882
Sperm retrieval rate by surgical interventions (micro-TESE) No of events	n = 59	n = 373

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided and no exclusion criteria reported)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI (91%) was reported))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Lo Giacco, 2014

Bibliographic Reference	Lo Giacco, Deborah; Chianese, Chiara; Sanchez-Curbelo, Josvany; Bassas, Lluis; Ruiz, Patricia; Rajmil, Osvaldo; Sarquella, Joaquim; Vives, Alvaro; Ruiz-Castane, Eduard; Oliva, Rafael; Ars, Elisabet; Krausz, Csilla; Clinical relevance of Y-linked CNV screening in male infertility: new insights based on the 8-year experience of a diagnostic genetic laboratory.; European journal of human genetics : EJHG; 2014; vol. 22 (no. 6); 754-61

Study details

Country/ies where study was carried out	Spain
Study type	Retrospective cohort study
Study dates	November 2004 - December 2012
Inclusion criteria	Infertile men who had Y chromosome microdeletion assessment
Exclusion criteria	Participants with unknown sperm parameters were excluded
Patient characteristics	N=11 Azoospermia AZFc microdeletion: 10 AZFa microdeletion: 1 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Clinic

Sources of funding	Not industry funded - The study was supported by the Spanish Health Ministry and the Spanish Ministry of Economy and Competitiveness
Other information	Complete or partial AZFc microdeletion: Participants had complete AZFc microdeletion. Surgical sperm retrieval method: Testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa microdeletion

Outcome	**AZFc microdeletion, N = 10**	**AZFa microdeletion, N = 1**
Sperm retrieval rate by surgical intervention (TESE) No of events	n = 1	n = 0

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure and Y chromosome microdeletion)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Mahdy, 2024

Bibliographic Reference	Mahdy, B.; La Croce, G.; Roscigno, M.; Manica, M.; Da Pozzo, L.; Sacca, A.; Microsurgical Testicular Sperm Extraction: Predictive Factors and Outcomes for Men with Nonobstructive Azoospermia; Andrologia; 2024; vol. 2024; 6380023

Study details

Country/ies where study was carried out	Italy
Study type	Retrospective cohort study

Study dates	April 2012 - February 2021
Inclusion criteria	Men with non-obstructive azoospermia who were referred to the male infertility outpatient clinic and underwent microdissection testicular sperm extraction procedure
Exclusion criteria	Obstructive azoospermia and other causes of male infertility, history of testicular cancer, patients who received radiation or chemotherapy in the past 6 months
Patient characteristics	N=172 Non-obstructive azoospermia AZFc microdeletion: 5 AZFb microdeletion: 1 AZFa microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 165 Male age in years; mean (SD): 37.5 (6.4) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa and AZFb microdeletion (isolated) Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Community hospital

Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa and AZFb microdeletion (isolated) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 5	AZFa and AZFb microdeletion (isolated), N = 2	Y chromosome microdeletion, N = 7	No Y chromosome microdeletion, N = 165
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 3	n = 0	n = 3	n = 122

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure and Y chromosome microdeletion)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(No information about prognostic factor measurement provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Mascarenhas, 2016

Bibliographic Reference	Mascarenhas, Mariano; Thomas, Sumi; Kamath, Mohan S; Ramalingam, Ramya; Kongari, Ann Marie; Yuvarani, S; Srivastava, Vivi M; George, Korula; Prevalence of chromosomal abnormalities and Y chromosome microdeletion among men with severe semen abnormalities and its correlation with successful sperm retrieval.; Journal of human reproductive sciences; 2016; vol. 9 (no. 3); 187-193

Study details

Country/ies where study was carried out	India
Study type	Prospective cohort study
Study dates	January 2010 - December 2014
Inclusion criteria	Males undergoing infertility evaluation with either non-obstructive azoospermia or severe oligozoospermia (concentration <5 million/ml)
Exclusion criteria	• obstructive azoospermia • obvious cause of testicular dysfunction such as gonadotoxic drug exposure and pituitary and hypothalamic causes
Patient characteristics	N=9 Non-obstructive azoospermia AZFc microdeletion: 2 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 2 AZFb microdeletion: 4 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFb microdeletion AZFc microdeletion AZFb + c microdeletion AZFa + b + c microdeletion

Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Tertiary care hospital
Sources of funding	No financial support or sponsorship received
Other information	Complete or partial AZF microdeletion: The study did not specify whether participants had complete or partial AZF microdeletions. Surgical sperm retrieval method: n=8 had testicular sperm aspiration (TESA) and n=1 had microdissection testicular sperm extraction done. Participants with AZFc (n=1 with KS), AZFa, b and c (n=1), and AZFb and c (n=1) microdeletions also had karyotypic abnormalities

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFb microdeletion vs AZFc microdeletion vs AZFb + c microdeletion vs AZFa + b + c microdeletion

Outcome	AZFb microdeletion, N = 4	AZFc microdeletion, N = 2	AZFb + c microdeletion, N = 2	AZFa + b + c microdeletion, N = 1
Sperm retrieval rate by surgical intervention (TESA and micro-TESE) TESA: testicular sperm aspiration No of events	n = 0	n = 2	n = 0	n = 0

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, however not reported if sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Miraghazadeh, 2019

Bibliographic Reference	Miraghazadeh, Azam; Sadighi Gilani, Mohammad Ali; Reihani-Sabet, Fakhredin; Ghaheri, Azadeh; Borjian Boroujeni, Parnaz; Zamanian, Mohammadreza; Detection of Partial AZFc Microdeletions in Azoospermic Infertile Men Is Not Informative of MicroTESE Outcome.; International journal of fertility & sterility; 2019; vol. 12 (no. 4); 298-302

Study details

Country/ies where study was carried out	Iran
Study type	Prospective cohort study
Study dates	2013 - 2014
Inclusion criteria	Infertile men with azoospermia or severe oligospermia who were candidates for micro-TESE surgery
Exclusion criteria	Infertile patients with: • obstructive azoospermia • varicocele • cryptorchidism • endocrine problems • history of chemotherapy or radiotherapy • abnormal karyotype
Patient characteristics	N=200 Non-obstructive azoospermia AZFc microdeletion: 16 No chromosomal abnormality: 184 Male age in years; mean (SD): 39.2 (6.4)

	Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Infertility centre
Sources of funding	Financially supported and performed at the Royan Institute for Reproductive Biomedicine
Other information	Complete or partial AZFc microdeletion: partial AZFc microdeletion Surgical sperm retrieval method: Microdissection testicular sperm extraction was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus No Y chromosome microdeletion

Outcome	**AZFc microdeletion, N = 16**	**No Y chromosome microdeletion, N = 184**
Sperm retrieval rate by surgical interventions (micro-TESE) No of events	n = 9	n = 81

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Valid and reliable measurement and clear definition of outcome reported, however sperm qualified for ICSI not reported)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Park, 2013

Bibliographic Reference	Park, Se Hwan; Lee, Hyo Serk; Choe, Jin Ho; Lee, Joong Shik; Seo, Ju Tae; Success rate of microsurgical multiple testicular sperm extraction and sperm presence in the ejaculate in korean men with y chromosome microdeletions.; Korean journal of urology; 2013; vol. 54 (no. 8); 536-40

Study details

Country/ies where study was carried out	Korea
Study type	Retrospective cohort study
Study dates	September 1997 - June 2012
Inclusion criteria	Infertile men with severe oligozoospermia (＜10×10^6 sperm/mL) or azoospermia who were screened for AZF deletion
Exclusion criteria	NR
Patient characteristics	N=58 Non-obstructive azoospermia AZFc microdeletion: 31 AZFb and c microdeletion: 14 AZFb microdeletion: 8 AZFa microdeletion: 5 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFa microdeletion AZFb microdeletion AZFc microdeletion

	AZFb + c microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	NR
Sources of funding	NR
Other information	Complete or partial AZF microdeletions: The study did not specify whether participants had complete or partial AZF microdeletions. Surgical sperm retrieval method: Microsurgical multiple testicular sperm extraction was used. None of AZF a + b + c deleted participants underwent surgical sperm retrieval procedure For all participants identified to have a Y chromosome microdeletion 2/168 had severe oligozoospermia but unclear if these participants included in the data analysed for this sample (n=58) where surgical sperm retrieval was attempted

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion vs AZFa microdeletion vs AZFb microdeletion vs AZFb + c microdeletion

Outcome	AZFc microdeletion, N = 31	AZFa microdeletion, N = 5	AZFb microdeletion, N = 8	AZFb + c microdeletion, N = 14
Sperm retrieval rate by surgical interventions (microsurgical multiple TESE) No of events	17	0	0	1

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, no exclusion criteria and setting reported)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Valid and reliable measurement and clear definition of outcome reported, however sperm qualified for ICSI was not reported)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Patrat, 2010

Bibliographic Reference	Patrat, Catherine; Bienvenu, Thierry; Janny, Laurent; Faure, Anne-Karen; Fauque, Patricia; Aknin-Seifer, Isabelle; Davy, Celine; Thiounn, Nicolas; Jouannet, Pierre; Levy, Rachel; Clinical data and parenthood of 63 infertile and Y-microdeleted men.; Fertility and sterility; 2010; vol. 93 (no. 3); 822-32

Study details

Country/ies where study was carried out	France
Study type	Retrospective cohort study
Study dates	June 1997 - July 2005
Inclusion criteria	Men consulting for infertility and classified as azoospermic (no spermatozoa), cryptoazoospermic (few spermatozoa), extreme oligozoospermic (sperm concentration >0–1.10^6 /mL), or severe oligozoospermic (sperm concentration >1–5.10^6 spermatozoa/mL)
Exclusion criteria	NR
Patient characteristics	N=27 Azoospermia AZFc microdeletion: 18 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 2 AZFb microdeletion: 6 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFb microdeletion

	AZFb + c microdeletion AZFa + b + c microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Multiple assisted reproduction centres
Sources of funding	NR
Other information	Complete or partial AZF microdeletions: complete AZFb microdeletion and complete AZFb + c microdeletion; but the study did not specify whether participants had complete or partial for other AZF microdeletions or AZFc microdeletion. Surgical sperm retrieval method: conventional (biopsy) testicular sperm extraction was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion vs AZFb microdeletion vs AZFb + c microdeletion vs AZFa + b + c microdeletion

Outcome	AZFc microdeletion, N = 18	AZFb microdeletion, N = 6	AZFb + c microdeletion, N = 2	AZFa + b + c microdeletion, N = 1
Sperm retrieval rate by surgical intervention (conventional -TESE) No of events	n = 6	n = 0	n = 0	n = 0

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, no exclusion criteria reported)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI was reported))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Schwarzer, 2016

Bibliographic Reference	Schwarzer, J U; Steinfatt, H; Schleyer, M; Kohn, F M; Fiedler, K; von Hertwig, I; Krusmann, G; Wurfel, W; Microdissection TESE is superior to conventional TESE in patients with nonobstructive azoospermia caused by Y chromosome microdeletions.; Andrologia; 2016; vol. 48 (no. 4); 402-5

Study details

Country/ies where study was carried out	Germany
Study type	Retrospective cohort study
Study dates	April 1996 - February 2005 for conventional TESE (N=11 patients) March 2005 - April 2015 for micro-TESE (N=14 patients)
Inclusion criteria	Male infertile patients with non-obstructive azoospermia and Y chromosome microdeletions in the AZF region undergoing TESE
Exclusion criteria	NR
Patient characteristics	N=25 Non-obstructive azoospermia AZFc microdeletion: 20 AZFb and c microdeletion: 2 AZFc and other chromosomic disorders: 2 AZFb microdeletion: 1 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFb microdeletion

	AZFb + c microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Outpatient hospital
Sources of funding	NR
Other information	Complete or partial AZF microdeletions: The study did not specify whether participants had complete or partial AZF microdeletions. Surgical sperm retrieval method: TESE (n=11) or micro-TESE (n=14)

AZF: azoospermia factor; BMI: body mass index; micro-TESE: microdissection testicular sperm extraction; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion vs AZFb mcirodeletion vs AZFb + c microdeletion

Outcome	AZFc microdeletion, N = 20	AZFb microdeletion, N = 1	AZFb + c microdeletion, N = 2
Sperm retrieval rate by surgical interventions (conventional multilocular TESE and micro-TESE) No of events	n = 10	n = 0	n = 0

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(No baseline characteristics of the study population, no exclusion criteria reported)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI was reported))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Sen, 2023

Bibliographic Reference	Sen, E.; Kizilkan, Y.; Duran, M.B.; Turunc, T.; Sahin, F.I.; Ozkardes, H.; Evaluation of the Genetic Analysis Results in Infertile Patients with Non-Obstructive Azoospermia; Journal of Urological Surgery; 2023; vol. 10 (no. 3); 233-237

Study details

Country/ies where study was carried out	Turkey
Study type	Retrospective cohort study
Study dates	NR
Inclusion criteria	Infertile male with non-obstructive azoospermia, genetic analysis results, and microdissection testicular sperm extraction procedure results, but no history of treatment for infertility, any assisted reproductive technique and urological operation
Exclusion criteria	Obstructive azoospermia, chemotherapy, radiotherapy, and participants who were lost to follow up, or whose information was not available from the hospital database
Patient characteristics	N=450 Non-obstructive azoospermia AZFc microdeletion: 12 AZFb microdeletion: 2 No chromosomal abnormality: 436 Male age in years; mean (SD): 33.3 (5.6) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFb microdeletion Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.

Duration of follow-up	NR
Setting	Hospital
Sources of funding	None
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFb microdeletion versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 12	AZFb microdeletion, N = 2	Y chromosome microdeletion, N = 14	No Y chromosome microdeletion, N = 436
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 4	n = 0	n = 4	n = 170

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and recruitment period not provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure and genetic analysis)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Participants had genetic analysis, but detailed information about the method was not provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Silber, 1998

Bibliographic Reference	Silber, S J; Alagappan, R; Brown, L G; Page, D C; Y chromosome deletions in azoospermic and severely oligozoospermic men undergoing intracytoplasmic sperm injection after testicular sperm extraction.; Human reproduction (Oxford, England); 1998; vol. 13 (no. 12); 3332-7

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	NR
Inclusion criteria	Men with non-obstructive azoospermia or with severe oligozoospermia (<1 x 10^6/ml in the ejaculate) who underwent Y-chromosomal sequence tagged site mapping and TESE-ICSI in attempt to conceive a child
Exclusion criteria	NR
Patient characteristics	N=51 Non-obstructive azoospermia AZFc microdeletion: 10 No Y chromosome microdeletion (other chromosomal abnormalities NR): 41 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	NR

Sources of funding	Supported by the National Institutes of Health D.C.P.
Other information	Complete or partial AZFc microdeletion: n=5 and n=5 had complete and partial AZFc microdeletion, respectively Surgical sperm retrieval method: conventional TESE

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	**AZFc microdeletion, N = 10**	**No Y chromosome microdeletion, N = 41**
Sperm retrieval rate by surgical interventions (conventional-TESE) No of events	n = 5	n = 22

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(No baseline characteristics of the study population, exclusion criteria, recruitment period and place reported; also TESE method not described)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Simoni, 2008

Bibliographic Reference	Simoni, Manuela; Tuttelmann, Frank; Gromoll, Jorg; Nieschlag, Eberhard; Clinical consequences of microdeletions of the Y chromosome: the extended Munster experience.; Reproductive biomedicine online; 2008; vol. 16 (no. 2); 289-303

Study details

Country/ies where study was carried out	Germany
Study type	Prospective cohort study
Study dates	November 1995 - May 2007

Inclusion criteria	Infertile men with non-obstructive azoospermia or severe oligozoospermia (<0.1 × 10^6 / ml) and with Y-chromosomal microdeletions
Exclusion criteria	NR
Patient characteristics	N=16 Azoospermia or severe oligozoospermia (proportion NR) AZFc microdeletion: 10 AZFb + c microdeletion: 2 AZFb microdeletion: 2 AZFa microdeletion: 2 Male age in years; mean (SD): 32.1 (6.4) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa microdeletion AZFb microdeletion AZFb + c microdeletion Partial AZFb microdeletion + AZFc microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	University hospital
Sources of funding	No financial conflict of interest

Other information	Complete or partial AZF microdeletions: AZF deletions and partial deletions of the AZFc region Surgical sperm retrieval method: conventional testicular sperm extraction (TESE) was used (bilateral testicular biopsy)

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion vs AZFa microdeletion vs AZFb microdeletion vs partial AZFb microdeletion + AZFc microdeletion

Outcome	AZFc microdeletion, N = 10	AZFa microdeletion, N = 2	AZFb microdeletion, N = 2	AZFb + c microdeletion, N = 1	Partial AZFb microdeletion + AZFc microdeletion, N = 1
Sperm retrieval rate by surgical intervention (TESE) No of events	n = 6	n = 0	n = 0	n = 0	n = 1

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided; no exclusion criteria reported)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI was reported))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Stahl, 2010 & 2011

Bibliographic Reference	Stahl, Peter J; Masson, Puneet; Mielnik, Anna; Marean, Michael B; Schlegel, Peter N; Paduch, Darius A; A decade of experience emphasizes that testing for Y microdeletions is essential in American men with azoospermia and severe oligozoospermia.; Fertility and sterility; 2010; vol. 94 (no. 5); 1753-6 Stahl, Peter J; Mielnik, Anna; Margreiter, Markus; Marean, Michael B; Schlegel, Peter N; Paduch, Darius A; Diagnosis of the gr/gr Y chromosome microdeletion does not help in the treatment of infertile American men.; The Journal of urology; 2011; vol. 185 (no. 1); 233-7

Study details

Country/ies where study was carried out	USA

Study type	Retrospective cohort study
Study dates	1997 - 2007
Inclusion criteria	Infertile men with sperm concentrations <5 million sperm/ml who underwent Y chromosome microdeletions assessment
Exclusion criteria	Obstructive azoospermia, chemotherapy, pelvic radiation therapy, cytogenetic abnormalities, cryptorchidism, congenital hypogonadism, Klinefelter's syndrome, patients who could not tested for gr/gr deletion, and patients without data on sperm concentration
Patient characteristics	N=448 Non-obstructive azoospermia AZFc microdeletion: 43 AZFa, b and c microdeletion: 4 AZFb and c microdeletion: 7 AZFb microdeletion: 7 AZFa microdeletion: 2 No chromosomal abnormality: 385 Male age in years; mean (SD): NR Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.

Duration of follow-up	NR
Setting	Male fertility clinic and genetics laboratory
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: n=21 and n=22 had complete and partial AZFc microdeletion, respectively Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 43	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 20	Y chromosome microdeletion, N = 63	No Y chromosome microdeletion, N = 385
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 29	n = 0	n = 29	n = 188

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI (particularly for those with AZFc microdeletion))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

AZF: azoospermia factor; ICSI: intracytoplasmic sperm injection

Tian, 2023

Bibliographic Reference	Tian, R.; Zhang, J.; Xu, Y.; Liu, S.; Deng, C.; Chen, H.; Li, P.; Huang, Y.; Zhi, E.; Liu, G.; Sun, G.; Liang, X.; Zhao, F.; Wu, Y.; Yao, C.; Zhang, W.; Li, Z.; Predicting Micro-TESE among Heterogeneous Nonobstructive Azoospermic Patients: The Impact on Surgical Decision and ICSI; Andrologia; 2023; vol. 2023; 4825062

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	March 2015 - August 2021
Inclusion criteria	Males with non-obstructive azoospermia who underwent micro-TESE
Exclusion criteria	Men: • with AZFa and/or AZFb deletions • those who had chemoradiotherapy • with any evidence of obstruction (e.g., history of vasectomy, congenital bilateral absence of the vas deferens) or ejaculation abnormality (e.g., low volume, decreased pH)
Patient characteristics	N=1822 Non-obstructive azoospermia AZFc microdeletion: 108 No Y chromosome microdeletion (included other chromosomal abnormalities): 1714 Male age in years; mean (SD): 30.9 (5.2) Duration of infertility in years; mean (SD): NR The study includes a development and an external validation cohort, the overall data from these 2 cohorts are reported here
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.

Duration of follow-up	NR
Setting	General hospital
Sources of funding	Supported by the Strategic Priority Research Program of the Chinese Academy of Sciences, Interdisciplinary Program of Shanghai Jiao Tong University, Clinical Research Innovation Plan of Shanghai General Hospital, and National Natural Science Foundation of China
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction was used. The no Y chromosome microdeletion group included n=1154 with idiopathic infertility (surgical sperm retrieval rate in this group: 352/1154), n=297 with KS, n=158 with undescended testes, and n=105 post-infectious disease

AZF: azoospermia factor; BMI: body mass index; KS: Klinefleter Syndrome; micro-TESE: microdissection testicular sperm extraction; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 108	No Y chromosome microdeletion, N = 1714
Sperm retrieval rate by surgical interventions (micro-TESE) No of events	n = 70	n = 679

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(No relevant baseline characteristics of the study population reported)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI was reported)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Tsujimura, 2004

Bibliographic Reference	Tsujimura, Akira; Matsumiya, Kiyomi; Takao, Tetsuya; Miyagawa, Yasushi; Koga, Minoru; Takeyama, Masami; Fujioka, Hideki; Okuyama, Akihiko; Clinical analysis of patients with azoospermia factor deletions by microdissection testicular sperm extraction.; International journal of andrology; 2004; vol. 27 (no. 2); 76-81

Study details

Country/ies where study was carried out	Japan
Study type	Retrospective cohort study
Study dates	October 2000 - August 2002
Inclusion criteria	Med diagnosed with non-obstructive azoospermia on the basis of a complete history, physical examination and endocrinological profile, and who were scheduled for TESE and sperm freezing
Exclusion criteria	Patients with chromosomal abnormalities.
Patient characteristics	N=57 AZFc microdeletion: 1 AZFa, b and c microdeletion: 1 AZFb and c microdeletion: 1 No Y chromosome microdeletion (other chromosomal abnormalities NR): 54 Male age in years; mean (SD): 32.4 (4.6) Duration of infertility in years; mean (SD): 3.5 (2.6)
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.

Duration of follow-up	NR
Setting	University hospital
Sources of funding	NR
Other information	Complete or partial AZF microdeletion: The participant in the AZFc group had partial AZFc microdeletion Surgical sperm retrieval method: Microdissection testicular sperm extraction was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation; TESE: testicular sperm extraction

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 1	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 2	Y chromosome microdeletion, N = 3	No Y chromosome microdeletion, N = 54
Sperm retrieval rate by surgical interventions (micro-TESE) No of events	n = 0	n = 0	n = 0	n = 20

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Valid and reliable measurement and clear definition of outcome reported but sperm qualified for ICSI was not reported)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Uzay, 2021

Bibliographic Reference	Uzay, Elif; Kizilay, Fuat; Altay, Baris; Akin, Haluk; Durmaz, Mehmet Burak; Investigation of genotype-phenotype correlation in patients with AZF microdeletion in a single-reference centre.; Andrologia; 2021; vol. 53 (no. 10); e14188

Study details

Country/ies where study was carried out	Turkey
Study type	Retrospective cohort study
Study dates	January 2009 - March 2019
Inclusion criteria	Patients with azoospermia
Exclusion criteria	NR
Patient characteristics	N=42 Azoospermia AZFc microdeletion: 31 AZFa, b and c microdeletion: 2 AZFb and c microdeletion: 4 AZFb microdeletion: 2 AZFa microdeletion: 3 Male age in years; mean (SD): 35.1 (7.1) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci)
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR

Setting	Hospital
Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction procedure was used.

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci)

Outcome	AZFc microdeletion, N = 31	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 11
Sperm retrieval rate by surgical intervention (micro-TESE) No of events	n = 16	n = 0

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported, and sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Yamaguchi, 2020

Bibliographic Reference	Yamaguchi, Kohei; Ishikawa, Tomomoto; Mizuta, Shimpei; Takeuchi, Takumi; Matsubayashi, Hidehiko; Kokeguchi, Shoji; Habara, Toshihiro; Ichioka, Kentaro; Ohashi, Masakazu; Okamoto, Sumihide; Kawamura, Toshihiro; Kanto, Satoru; Taniguchi, Hisanori; Tawara, Fumiko; Hara, Tetsuaki; Hibi, Hatsuki; Masuda, Hiroshi; Matsuyama, Takehiko; Yoshida, Hiroaki; Clinical outcomes of microdissection testicular sperm extraction and intracytoplasmic sperm injection in Japanese men with Y chromosome microdeletions.; Reproductive medicine and biology; 2020; vol. 19 (no. 2); 158-163

Study details

Country/ies where study was carried out	Japan
Study type	Retrospective cohort study
Study dates	2007 - 2017
Inclusion criteria	Infertile azoospermic and very severe oligozoospermic (a sperm counts of <1 million per mL) men
Exclusion criteria	NR
Patient characteristics	N=584 Non-obstructive azoospermia AZFc microdeletion: 50 No Y chromosome microdeletion (other chromosomal abnormalities NR): 534 Male age in years; mean (SD): 34.1 (5.5) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Multiple reproductive centres

Sources of funding	NR
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction was used

AZF: azoospermia factor; BMI: body mass index; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	**AZFc microdeletion, N = 50**	**No Y chromosome microdeletion, N = 534**
Sperm retrieval rate by surgical interventions (micro-TESE) No of events	n = 33	n = 105

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided and no exclusion criteria reported)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI was reported))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Zeadna, 2020

Bibliographic Reference	Zeadna, A.; Khateeb, N.; Rokach, L.; Lior, Y.; Har-Vardi, I.; Harlev, A.; Huleihel, M.; Lunenfeld, E.; Levitas, E.; Prediction of sperm extraction in non-obstructive azoospermia patients: A machine-learning perspective; Human Reproduction; 2020; vol. 35 (no. 7); 1505-1514

Study details

Country/ies where study was carried out	Israel
Study type	Retrospective cohort study

Study dates	1995 - 2017
Inclusion criteria	Patients with non-obstructive azoospermia referred to the IVF unit for conventional testicular sperm extraction procedure
Exclusion criteria	Patients with chemotherapy, radiotherapy, and hypogonadotropic hypogonadism
Patient characteristics	N=119 Non-obstructive azoospermia AZFc microdeletion: 3 AZFa microdeletion: 1 No Y chromosome microdeletion (included other chromosomal abnormalities): 115 Male age in years; mean (SD): 33.0 (7.8) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion AZFa or AZFb microdeletion (isolated or in combination with other loci) Y chromosome microdeletion No Y chromosome microdeletion
Confounding factor(s) of interest	Multivariate logistic regression model was used (that adjust for age, FSH, testosterone level, mean testicular volume and active smoking). In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	IVF unit at a medical centre
Sources of funding	Not industry funded - The study was supported by the Division of Obstetrics and Gynecology, Soroka University Medical Centre.

Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Conventional testicular sperm extraction procedure was used. The no Y chromosome microdeletion group included n=8 with KS

AZF: azoospermia factor; BMI: body mass index; KS: Klinefelter Syndrome; IVF: invitro fertilisation; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus AZFa or AZFb microdeletion (isolated or in combination with other loci) versus Y chromosome microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 3	AZFa or AZFb microdeletion (isolated or in combination with other loci), N = 1	Y chromosome microdeletion, N = 4	No Y chromosome microdeletion, N = 115
Sperm retrieval rate by surgical intervention (conventional TESE) No of events	n = 2	n = 0	n = 2	n = 76

AZF: azoospermia factor; TESE: testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided, and exclusion criteria not provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants who had surgical sperm retrieval procedure)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(No information about prognostic factor measurement reported)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description of the valid and reliable measurement of outcome reported, but unclear whether sperms were suitable for ICSI)*
Study Confounding	Study Confounding Summary	Low risk of bias *(Multivariate logistic regression was used (and adjusted for potential confounders))*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

ICSI: intracytoplasmic sperm injection

Zhang, 2021

Bibliographic Reference	Zhang, Hong-Liang; Zhao, Lian-Ming; Mao, Jia-Ming; Liu, De-Feng; Tang, Wen-Hao; Lin, Hao-Cheng; Zhang, Li; Lian, Ying; Hong, Kai; Jiang, Hui; Sperm retrieval rates and clinical outcomes for patients with different causes of azoospermia who undergo microdissection testicular sperm extraction-intracytoplasmic sperm injection.; Asian journal of andrology; 2021; vol. 23 (no. 1); 59-63

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	January 2014 - December 2017
Inclusion criteria	Men with non-obstructive azoospermia who underwent micro-TESE-ICSI and who: • had complete clinical data; • had no pre-existing chronic diseases, including hypertension, diabetes mellitus, and heart, kidney, haematological, and autoimmune diseases; • had no female infertility factors, including anovulation, hormonal infertility, tubal factors, and endometriosis; • age between 23 to 35 years; • BMI from 18 kg m^2 to 30 kg m^2
Exclusion criteria	NR
Patient characteristics	N=769 Non-obstructive azoospermia AZFc microdeletion: 91 No Y chromosome microdeletion (included other chromosomal abnormalities): 678 Male age in years; mean (SD): 30.1 (4.7) Duration of infertility in years; mean (SD): NR
Risk factor(s) of interest	AZFc microdeletion No Y chromosome microdeletion

Confounding factor(s) of interest	The study did not adjust for confounding factors. In this review we did not specify confounding factors of interest.
Duration of follow-up	NR
Setting	Hospital
Sources of funding	Funded by the National Key Research and Development Project, National Key Research and Development Project, National Key Research and Developmental Program of China, Young Scientists Fund of the National Natural Science Foundation of China, Clinical Medicine PlusX-Young Scholars Project, Peking University, Beijing Municipal Natural Science Foundation, and National Key Research and Development Program of China
Other information	Complete or partial AZFc microdeletion: The study did not specify whether participants had complete or partial AZFc microdeletion. Surgical sperm retrieval method: Microdissection testicular sperm extraction was used. The no Y chromosome microdeletion group included n=319 with idiopathic infertility (surgical sperm retrieval rate in this group: 98/319), n=284 with KS, n=52 with undescended testes, and n=23 post-infectious disease

AZF: azoospermia factor; BMI: body mass index; KS: Klinefelter Syndrome; ICSI: intracytoplasmic sperm injection; micro-TESE: microdissection testicular sperm extraction; NR: not reported; SD: standard deviation

Outcomes

AZFc microdeletion versus no Y chromosome microdeletion

Outcome	AZFc microdeletion, N = 91	No Y chromosome microdeletion, N = 678
Sperm retrieval rate by surgical interventions (micro-TESE) No. of events for No Y chromosome microdeletion group calculated by the technical team based on the % reported in the paper No of events	n = 67	n = 287

AZF: azoospermia factor; micro-TESE: microdissection testicular sperm extraction

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided and no exclusion criteria reported)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data were available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of prognostic factor provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement and clear definition of outcome reported (sperm qualified for ICSI was reported))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

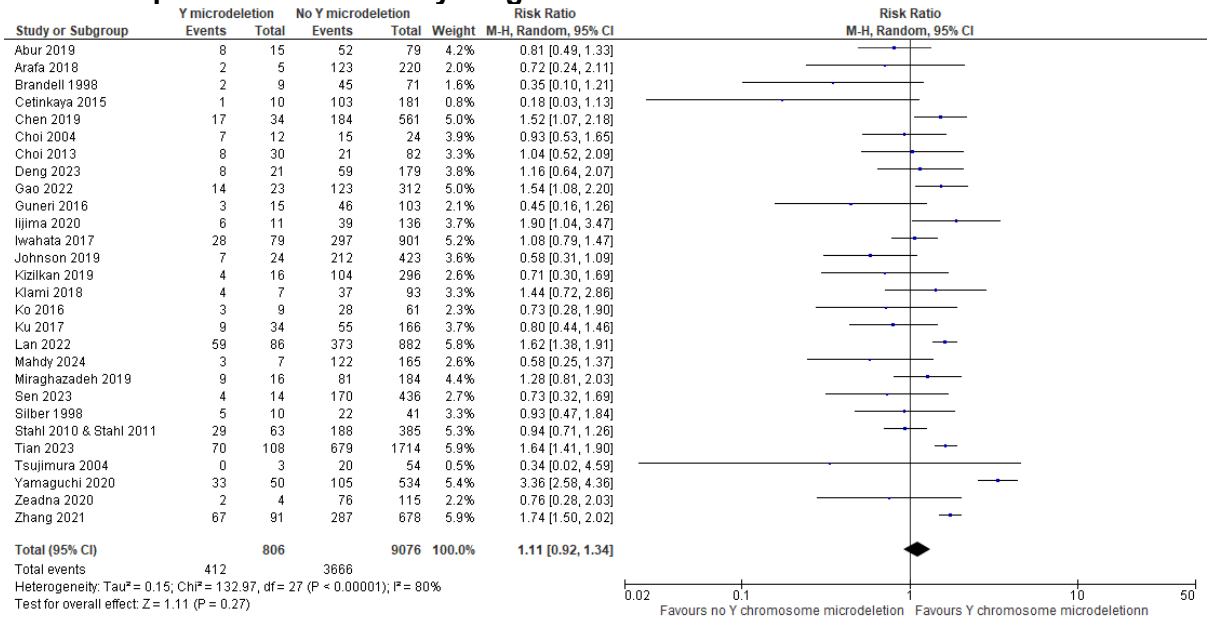
ICSI: intracytoplasmic sperm injection

Appendix E Forest plots

Forest plots for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

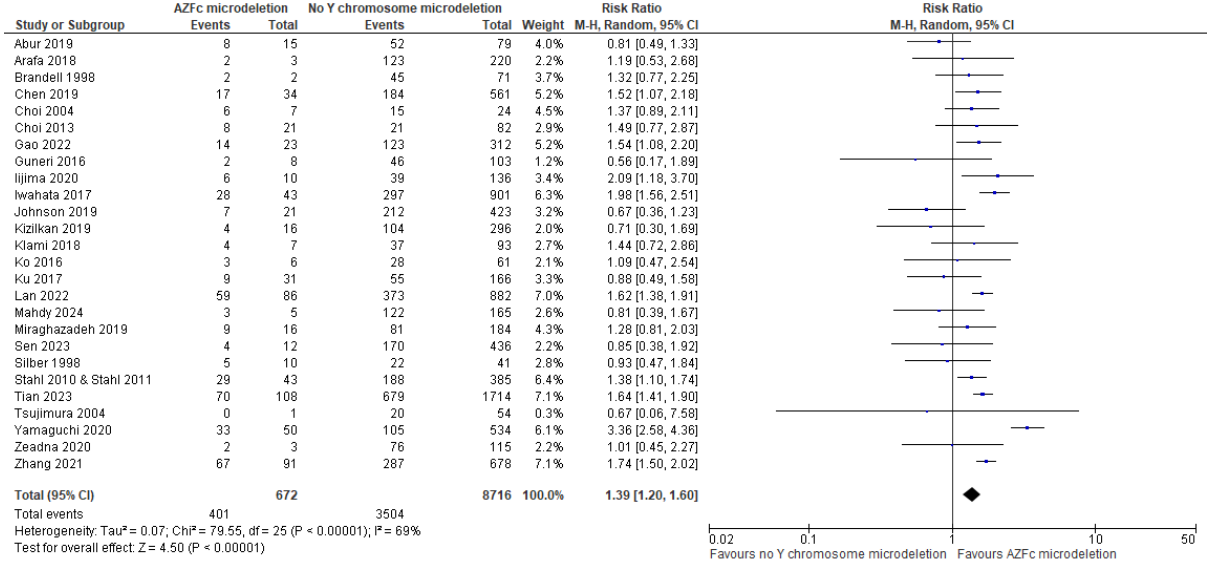
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Y chromosome microdeletion (any) versus no Y chromosome microdeletion: sperm retrieval rate by surgical intervention



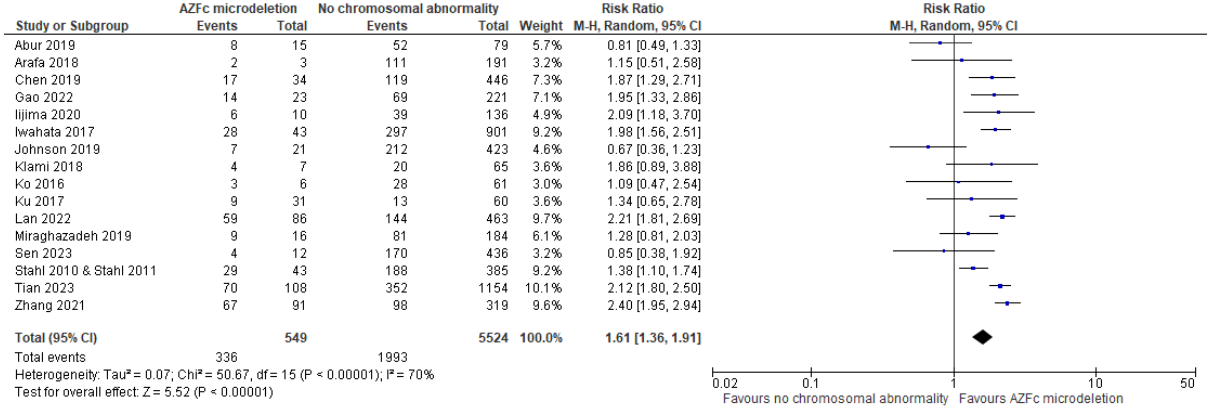
AZF: azoospermia factor; CI: confidence interval; M-H: Mantel-Haenszel

Figure 3: AZFc microdeletion (isolated) versus no Y chromosome microdeletion: sperm retrieval rate by surgical intervention



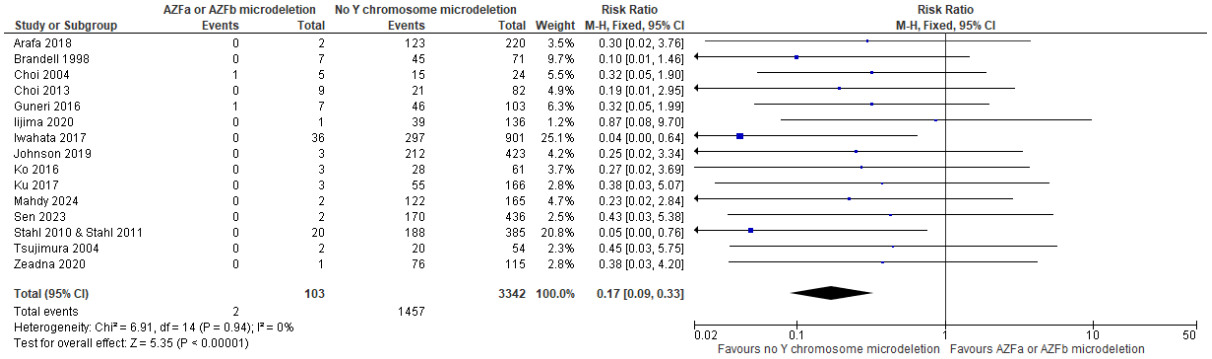
AZF: azoospermia factor; CI: confidence interval; M-H: Mantel-Haenszel

Figure 4: AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis): sperm retrieval rate by surgical intervention



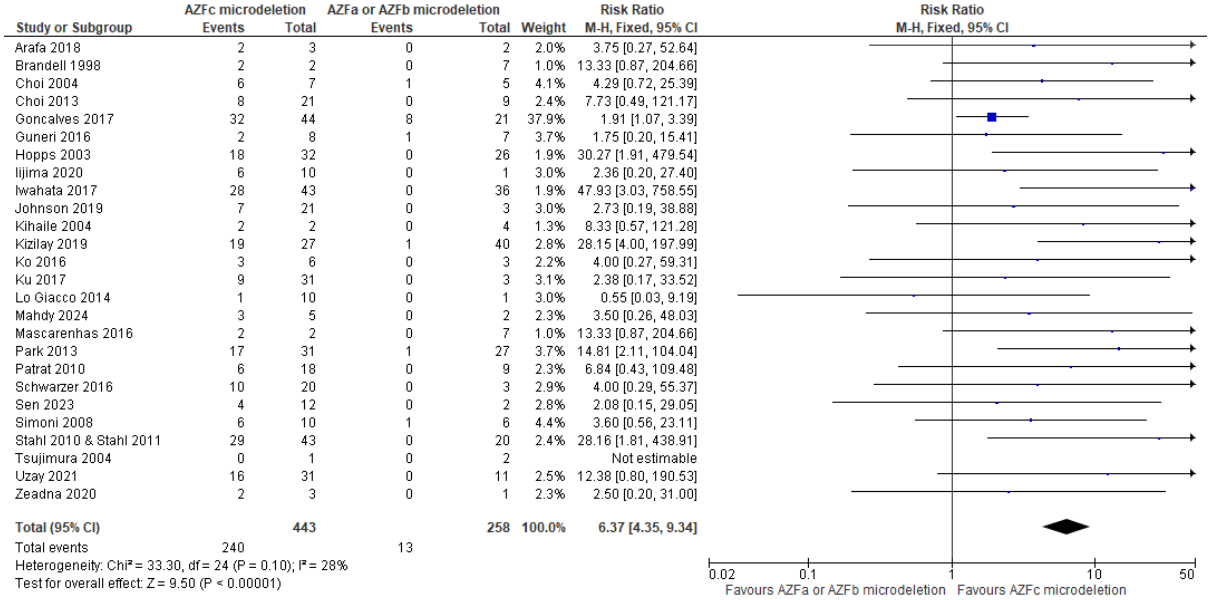
AZF: azoospermia factor; CI: confidence interval; M-H: Mantel-Haenszel

Figure 5: AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion: sperm retrieval rate by surgical intervention



AZF: azoospermia factor; CI: confidence interval; M-H: Mantel-Haenszel

Figure 6: AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci): sperm retrieval rate by surgical intervention



AZF: azoospermia factor; CI: confidence interval; M-H: Mantel-Haenszel

Appendix F GRADE tables

GRADE tables for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

Table 5: Evidence profile for comparison between Y chromosome microdeletion (any) versus no Y chromosome microdeletion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Y chromosome microdeletion (any)	No Y chromosome microdeletion	Relative (95% CI)	Absolute		
Sperm retrieval rate by surgical intervention												
28[1]	observational studies	very serious[2]	serious[3]	no serious indirectness	serious[4]	none	412/806 (51.1%)	3666/9076 (40.4%)	RR 1.11 (0.92 to 1.34)	44 more per 1000 (from 32 fewer to 137 more)	VERY LOW	CRITICAL

AZF: azoospermia factor; CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1] Studies included in analysis: Abur 2019; Arafa 2018; Brandell 1998; Cetinkaya 2015; Chen 2019; Choi 2004; Choi 2013; Deng 2023; Gao 2022; Guneri 2016; Iijima 2020; Iwahata 2017; Johnson 2019; Kizilkan 2019; Klami 2018; Ko 2016; Ku 2017; Lan 2022; Mahdy 2024; Miraghazadeh 2019; Sen 2023; Silber 1998; Stahl 2010 & 2011; Tian 2023; Tsujimura 2004; Yamaguchi 2020; Zeadna 2020; Zhang 2021

[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS

[3] Serious heterogeneity unexplained by subgroup analysis

[4] 95% CI crosses 1 MID

Table 6: Evidence profile for comparison between AZFc microdeletion (isolated) versus no Y chromosome microdeletion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZFc microdeletion (isolated)	No Y chromosome microdeletion	Relative (95% CI)	Absolute		
Sperm retrieval rate by surgical intervention												
26[1]	observational studies	serious[2]	serious[3]	no serious indirectness	serious[4]	none	401/672 (59.7%)	3504/8716 (40.2%)	RR 1.39 (1.2 to 1.6)	157 more per 1000 (from 80 more to 241 more)	VERY LOW	CRITICAL

AZF: azoospermia factor; CI: confidence interval; MID: minimally important difference; RR: risk ratio
[1] Studies included in analysis: Abur 2019; Arafa 2018; Brandell 1998; Chen 2019; Choi 2004; Choi 2013; Gao 2022; Guneri 2016; Iijima 2020; Iwahata 2017; Johnson 2019; Kizilkan 2019; Klami 2018; Ko 2016; Ku 2017; Lan 2022; Mahdy 2024; Miraghazadeh 2019; Sen 2023; Silber 1998; Stahl 2010 & 2011; Tian 2023; Tsujimura 2004; Yamaguchi 2020; Zeadna 2020; Zhang 2021
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[3] Serious heterogeneity unexplained by subgroup analysis
[4] 95% CI crosses 1 MID

Table 7: Evidence profile for comparison between AZFc microdeletion (isolated) versus no chromosomal abnormality (sensitivity analysis)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZFc microdeletion (isolated)	No chromosomal abnormality	Relative (95% CI)	Absolute		
Sperm retrieval rate by surgical intervention												
16[1]	observational studies	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	336/549 (61.2%)	1993/5524 (36.1%)	RR 1.61 (1.36 to 1.91)	220 more per 1000 (from 130 more to 328 more)	VERY LOW	CRITICAL

AZF: azoospermia factor; CI: confidence interval; MID: minimally important difference; RR: risk ratio
[1] Studies included in analysis: Abur 2019; Arafa 2018; Chen 2019; Gao 2022; Iijima 2020; Iwahata 2017; Johnson 2019; Klami 2018; Ko 2016; Ku 2017; Lan 2022; Miraghazadeh 2019; Sen 2023; Stahl 2010 & 2011; Tian 2023; Zhang 2021
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[3] Serious heterogeneity unexplained by subgroup analysis

Table 8: Evidence profile for comparison between AZFa or AZFb microdeletion (isolated or in combination with other loci) versus no Y chromosome microdeletion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZFa or AZFb microdeletion (isolated or in combination with other loci)	No Y chromosome microdeletion	Relative (95% CI)	Absolute		
Sperm retrieval rate by surgical intervention												
15[1]	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/103 (1.9%)	1457/3342 (43.6%)	RR 0.17 (0.09 to 0.33)	362 fewer per 1000 (from 292 fewer to 397 fewer)	VERY LOW	CRITICAL

AZF: azoospermia factor; CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1] Studies included in analysis: Arafa 2018; Brandell 1998; Choi 2004; Choi 2013; Guneri 2016; Iijima 2020; Iwahata 2017; Johnson 2019; Ko 2016; Ku 2017; Mahdy 2024; Sen 2023; Stahl 2010 & 2011; Tsujimura 2004; Zeadna 2020

[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Table 9: Evidence profile for comparison between AZFc microdeletion (isolated) versus AZFa or AZFb microdeletion (isolated or in combination with other loci)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZFc microdeletion (isolated)	AZFa or AZFb microdeletion (isolated or in combination with other loci)	Relative (95% CI)	Absolute		
Sperm retrieval rate by surgical intervention												
26[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	240/443 (54.2%)	13/258 (5%)	RR 6.37 (4.35 to 9.34)	271 more per 1000 (from 169 more to 420 more)[3]	VERY LOW	CRITICAL

AZF: azoospermia factor; CI: confidence interval; MID: minimally important difference; RR: risk ratio

[1] Studies included in analysis: Arafa 2018; Brandell 1998; Choi 2004; Choi 2013; Goncalves 2017; Guneri 2016; Hopps 2003; Iijima 2020; Iwahata 2017; Johnson 2019; Kihaile 2004; Kizilay 2019; Ko 2016; Ku 2017; Lo Giacco 2014; Mahdy 2024; Mascarenhas 2016; Park 2013; Patrat 2010; Schwarzer 2016; Sen 2023; Simoni 2008; Stahl 2010 & 2011; Tsujimura 2004; Uzay 2021; Zeadna 2020

[2] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS

[3] 1 study was not included (not estimable) in RR calculation as it was a double-arm-zero-events study, but included in absolute effect calculation (Tsujimura 2004)

Appendix G Economic evidence study selection

No health economic search was conducted for this review question as this was a prognostic review.

Appendix H Economic evidence tables

No evidence was identified which was applicable to this review question.

Appendix I Economic model

No health economic modelling was undertaken for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

Excluded prognostic studies

Table 10: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Ando, M., Yamaguchi, K., Chiba, K. et al. (2013) Outcome of microdissection testicular sperm extraction in azoospermic patients with Klinefelter syndrome and other sex-chromosomal anomalies. Systems Biology in Reproductive Medicine 59(4): 210-213	- Population not in PICO *Participants with Klinefelter syndrome and other sex-chromosome abnormalities*
Arshad, Muhammad A; Majzoub, Ahmad; Esteves, Sandro C (2020) Predictors of surgical sperm retrieval in non-obstructive azoospermia: summary of current literature. International urology and nephrology 52(11): 2015-2038	- Study design not in PICO *Narrative review*
Bonarriba, C R, Burgues, J P, Vidana, V et al. (2013) Predictive factors of successful sperm retrieval in azoospermia. Actas urologicas espanolas 37(5): 266-72	- Study not reported in English
Caroppo, Ettore and Colpi, Giovanni Maria (2021) Prediction Models for Successful Sperm Retrieval in Patients with Non-Obstructive Azoospermia Undergoing Microdissection Testicular Sperm Extraction: Is There Any Room for Further Studies?. Journal of clinical medicine 10(23)	- Study design not in PICO *Narrative review*
Carpinello, Olivia J, Marinaro, Jessica, Hill, Micah J et al. (2021) Karyotypic abnormalities and Y chromosome microdeletions: How do these impact in vitro fertilization outcomes, and how common are they in the modern in vitro fertilization practice?. F&S reports 2(3): 300-307	- Data cannot be extracted
Cissen, M, Meijerink, A M, D'Hauwers, K W et al. (2016) Prediction model for obtaining spermatozoa with testicular sperm extraction in men with non-obstructive azoospermia. Human reproduction (Oxford, England) 31(9): 1934-41	- Data cannot be extracted
Colaco, Stacy and Modi, Deepak (2024) Azoospermia factor c microdeletions and outcomes of assisted reproductive technology: a systematic review and meta-analysis. Fertility and sterility 121(1): 63-71	- Systematic review, included studies checked for relevance

Study	Code [Reason]
Colpi, G M, Piediferro, G, Nerva, F et al. (2005) Sperm retrieval for intra-cytoplasmic sperm injection in non-obstructive azoospermia. Minerva urologica e nefrologica = The Italian journal of urology and nephrology 57(2): 99-107	- Study design not in PICO *Narrative review*
Corona, G, Minhas, S, Giwercman, A et al. (2019) Sperm recovery and ICSI outcomes in men with non-obstructive azoospermia: a systematic review and meta-analysis. Human reproduction update 25(6): 733-757	- Systematic review, included studies checked for relevance
Degheili, Jad A, Yacoubian, Aline A, Abu Dargham, Rana H et al. (2022) Prevalence of Y-chromosomal microdeletions and karyotype abnormalities in a cohort of Lebanese infertile men. Urology annals 14(1): 48-52	- Data cannot be extracted
Donker, R B, Vloeberghs, V, Groen, H et al. (2017) Chromosomal abnormalities in 1663 infertile men with azoospermia: the clinical consequences. Human reproduction (Oxford, England) 32(12): 2574-2580	- Data cannot be extracted
Emirdar, Volkan and Acet, Ferruh (2023) The effect of azoospermia factor microdeletions on intracytoplasmic sperm injection results in azoospermia patients. Pakistan journal of medical sciences 39(3): 672-676	- Outcome not in PICO *Pregnancy rate and number of oocytes retrieved, but not sperm retrieval rate, reported*
Glina, Sidney and Vieira, Marcelo (2013) Prognostic factors for sperm retrieval in non-obstructive azoospermia. Clinics (Sao Paulo, Brazil) 68suppl1: 121-4	- Study design not in PICO *Narrative review*
Golin, Andrew P; Yuen, Wallace; Flannigan, Ryan (2021) The effects of Y chromosome microdeletions on in vitro fertilization outcomes, health abnormalities in offspring and recurrent pregnancy loss. Translational andrology and urology 10(3): 1457-1466	- Study design not in PICO *Narrative review*
Hibi, Hatsuki, Sugie, Miho, Sonohara, Megumi et al. (2023) Infertility treatment for patients having a microdeletion of azoospermic factor (AZF). Nagoya journal of medical science 85(2): 233-240	- Data cannot be extracted
Huang, I-Shen, Chen, Wei-Jen, Li, Li-Hua et al. (2022) The predictive factors of successful sperm retrieval for men with Y chromosome AZFc microdeletion. Journal of assisted reproduction and genetics 39(10): 2395-2401	- Study design not in PICO *Non-comparative study*
Huang, I-Shen, Fantus, Richard J, Chen, Wei-Jen et al. (2020) Do partial AZFc deletions affect the sperm retrieval rate in non-mosaic Klinefelter patients undergoing microdissection testicular sperm extraction?. BMC urology 20(1): 21	- Population not in PICO *Population restricted to those with Klinefelter syndrome*

Study	Code [Reason]
Ishikawa T, Mizutu S YKEA (2016) Clinical consequences of microdeletions of y chromosome in Japanese non-obstructive azoospermic patients. Fertil Steril 106: e295	- Conference abstract.
Ishikawa, T (2012) Surgical recovery of sperm in non-obstructive azoospermia. Asian journal of andrology 14(1): 109-15	- Study design not in PICO *Narrative review*
Jiao, Zhong-Yu, Li, Mao-Ran, Zhuo, Lin et al. (2023) Sperm retrieval rate and patient factors in azoospermia factor c microdeletion azoospermia: a systematic review. BJU international	- Systematic review, included studies checked for relevance
Kalsi, Jas, Thum, Meen-Yau, Muneer, Asif et al. (2012) In the era of micro-dissection sperm retrieval (m-TESE) is an isolated testicular biopsy necessary in the management of men with non-obstructive azoospermia?. BJU international 109(3): 418-24	- Data cannot be extracted
Kilic, S., Yuksel, B., Yilmaz, N. et al. (2009) Results of ICSI in severe oligozoospermic and azoospermic patients with AZF microdeletions. Iranian Journal of Reproductive Medicine 7(2): 79-84	- Data cannot be extracted *Sperm retrieval rate by surgical interventions and spermium in the ejaculate were not reported separately*
Kim, Min Jee, Choi, Hye Won, Park, So Yeon et al. (2012) Molecular and cytogenetic studies of 101 infertile men with microdeletions of Y chromosome in 1,306 infertile Korean men. Journal of assisted reproduction and genetics 29(6): 539-46	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Kleiman, S.E., Yogev, L., Lehavi, O. et al. (2011) The likelihood of finding mature sperm cells in men with AZFb or AZFb-c deletions: Six new cases and a review of the literature (1994-2010). Fertility and Sterility 95(6): 2005-2012e4	- Study design not in PICO *Case report and literature review*
Li Zhang, Ph.D (2012) Effect of Age on Sperm Recovery of Microdissection Testicular Sperm Extraction in Nonobstructive Azoospermia Patients. clinicaltrials.gov	- Study design not in PICO *Study protocol registered in Clinicaltrials.gov*
Majzoub, Ahmad, Arafa, Mohamed, Clemens, Hailey et al. (2022) A systemic review and meta-analysis exploring the predictors of sperm retrieval in patients with non-obstructive azoospermia and chromosomal abnormalities. Andrologia 54(3): e14303	- Systematic review, included studies checked for relevance
Mohammed, F, Al-Yatama, F, Al-Bader, M et al. (2007) Primary male infertility in Kuwait: a cytogenetic and molecular study of 289 infertile Kuwaiti patients. Andrologia 39(3): 87-92	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Okutman-Emonts, O, Pehlivan, S, Tavmergen, E et al. (2004) Screening of Y chromosome microdeletion which contains AZF regions in 71 Turkish azoospermic men. Genetic counseling (Geneva, Switzerland) 15(2): 199-205	- Outcome not in PICO *Surgical sperm retrieval rate not reported*

Study	Code [Reason]
Olesen, Inge Ahlmann, Andersson, Anna-Maria, Aksglaede, Lise et al. (2017) Clinical, genetic, biochemical, and testicular biopsy findings among 1,213 men evaluated for infertility. Fertility and sterility 107(1): 74-82e7	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Oliva, R, Margarit, E, Ballesca, J L et al. (1998) Prevalence of Y chromosome microdeletions in oligospermic and azoospermic candidates for intracytoplasmic sperm injection. Fertility and sterility 70(3): 506-10	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Oz, Ozlem (2021) Evaluation of Y chromosome microdeletions and chromosomal anomalies in infertile men. Hormone molecular biology and clinical investigation 42(3): 279-283	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Pantke, P., Diemer, T., Marconi, M. et al. (2008) Testicular Sperm Retrieval in Azoospermic Men. European Urology, Supplements 7(12): 703-714	- Study design not in PICO *Narrative review*
Pavan-Jukic, Doroteja, Stubljar, David, Jukic, Tomislav et al. (2020) Predictive factors for sperm retrieval from males with azoospermia who are eligible for testicular sperm extraction (TESE). Systems biology in reproductive medicine 66(1): 70-75	- Data cannot be extracted
Peterlin, B, Kunej, T, Sinkovec, J et al. (2002) Screening for Y chromosome microdeletions in 226 Slovenian subfertile men. Human reproduction (Oxford, England) 17(1): 17-24	- Data cannot be extracted
Purificación Hernández-Vargas, PhD (2015) Aneuploidies in Embryos and Spermatozoa From Patients With Y-chromosome Microdeletions. clinicaltrials.gov	- Study design not in PICO *Study protocol registered in Clinicaltrials.gov*
Quilter, Claire R, Svennevik, Elizabeth C, Serhal, Paul et al. (2003) Cytogenetic and Y chromosome microdeletion screening of a random group of infertile males. Fertility and sterility 79(2): 301-7	- Outcome not in PICO *Sperm retrieval rate by surgical interventions not reported*
Raicu, Florina, Popa, L, Apostol, Pompilia et al. (2003) Screening for microdeletions in human Y chromosome--AZF candidate genes and male infertility. Journal of cellular and molecular medicine 7(1): 43-8	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
RAO, M.V., Shah, N.P., Raval, R.J. et al. (2021) Current status of y chromosome microdeletions: Prevalence, distribution, implication and association with male infertility in indian men- a review. Journal of Clinical and Diagnostic Research 15(3): ge01-ge09	- Study design not in PICO *Narrative review*
Rucker, G B, Mielnik, A, King, P et al. (1998) Preoperative screening for genetic abnormalities in	- Outcome not in PICO *Surgical sperm retrieval rate not reported*

Study	Code [Reason]
men with nonobstructive azoospermia before testicular sperm extraction. The Journal of urology 160(6pt1): 2068-71	
Sabbaghian, Marjan, Mohseni Meybodi, Anahita, Rafaee, Alemeh et al. (2018) Sperm retrieval rate and reproductive outcome of infertile men with azoospermia factor c deletion. Andrologia 50(7): e13052	- Study design not in PICO *Non-comparative*
Saber-Khalaf, M.; Ali, A.F.; Elsoghier, O.M. (2022) Predictive factors of successful testicular sperm extraction for non-obstructive azoospermia with a history of bilateral cryptorchidism and normal testosterone. Andrologia 54(1): e14284	- Data cannot be extracted *Data not reported for participants with Y chromosome microdeletions*
Salihu, Hamisu M and Aliyu, Muktar H (2003) Sperm retrieval in infertile males: comparison between testicular sperm extraction and testicular sperm aspiration techniques. Wiener klinische Wochenschrift 115(11): 370-9	- Study design not in PICO *Literature review*
Salvarci, Ahmet; Gurbuz, Ali Sami; Balasar, Mehmet (2020) Evaluation from a different perspective of 10-year results of infertile males with Y chromosome AZFc microdeletions compared with a control group. Andrologia 52(6): e13572	- Comparison not in PICO
Shah, Rupin and Gupta, Chirag (2018) Advances in sperm retrieval techniques in azoospermic men: A systematic review. Arab journal of urology 16(1): 125-131	- Study design not in PICO *Not a systematic review (although the authors stated that it is a systematic review, but they did not follow systematic approach)*
Spahovic, Hajrudin, Goktolga, Umit, Junuzovic, Dzelaludin et al. (2017) Evaluation of Prognostic Factors and Determinants in Surgical Sperm Retrieval Procedures in Azoospermic Patients. Medical archives (Sarajevo, Bosnia and Herzegovina) 71(4): 243-245	- Comparison not in PICO
Stouffs, Katrien, Tournaye, Herman, Van der Elst, Josiane et al. (2008) Do we need to search for gr/gr deletions in infertile men in a clinical setting?. Human reproduction (Oxford, England) 23(5): 1193-9	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Suganthi, Ramaswamy, Vijesh, Vv, Jayachandran, Sanjay et al. (2013) Multiplex PCR based screening for microdeletions in azoospermia factor region of Y chromosome in azoospermic and severe oligozoospermic south Indian men. Iranian journal of reproductive medicine 11(3): 219-26	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Tabassum Siddiqui, Rubina; Mujtaba, Nosheen; Naz, Mamoona (2013) The prevalence of Y chromosome microdeletions in Pakistani infertile men. Iranian journal of reproductive medicine 11(8): 619-24	- Outcome not in PICO *Surgical sperm retrieval rate not reported*

Study	Code [Reason]
The Trinh, Son, Nguyen, Nhat Ngoc, Thi Thu Le, Hien et al. (2023) Screening Y Chromosome Microdeletion in 1121 Men with Low Sperm Concentration and the Outcomes of Microdissection Testicular Sperm Extraction (mTESE) for Sperm Retrieval from Azoospermic Patients. The application of clinical genetics 16: 155-164	- Comparison not in PICO *Sperm retrieval rate reported for participants with AZFc microdeletion, but not for comparison group*
Visser, L, Westerveld, G H, Korver, C M et al. (2009) Y chromosome gr/gr deletions are a risk factor for low semen quality. Human reproduction (Oxford, England) 24(10): 2667-73	- Systematic review, included studies checked for relevance
Yamaguchi K, Ishikawa T, Mizuta S TT (2015) Clinical assessment of microdissection testicular sperm extraction in Japanese patients with Y chromosome microdeletions. 104: e44-5	- Study design not in PICO *Conference abstract*
Yogev, Leah, Segal, Shmuel, Zeharia, Einav et al. (2004) Sex chromosome alignment at meiosis of azoospermic men with azoospermia factor microdeletion. Journal of andrology 25(1): 110-6	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Yuen, Wallace, Golin, Andrew P, Flannigan, Ryan et al. (2021) Histology and sperm retrieval among men with Y chromosome microdeletions. Translational andrology and urology 10(3): 1442-1456	- Systematic review, included studies checked for relevance
Zarrabi, A D and Kruger, T F (2021) Microsurgical testicular sperm extraction for testicular failure: the South African experience and first successful pregnancy. South African journal of surgery. Suid-Afrikaanse tydskrif vir chirurgie 59(2): 52-56	- Data cannot be extracted *Sperm retrieval rate not reported separately for those with Y chromosome microdeletion*
Zhang, Fengbin, Li, Lejun, Wang, Liquan et al. (2013) Clinical characteristics and treatment of azoospermia and severe oligospermia patients with Y-chromosome microdeletions. Molecular reproduction and development 80(11): 908-15	- Outcome not in PICO *Surgical sperm retrieval rate not reported*
Zhang, Li, Mao, Jia-Ming, Li, Ming et al. (2021) Poor intracytoplasmic sperm injection outcome in infertile males with azoospermia factor c microdeletions. Fertility and sterility 116(1): 96-104	- Data cannot be extracted
Zhu, Yuan-Chang, Wu, Tong-Hua, Li, Guan-Gui et al. (2015) Decrease in fertilization and cleavage rates, but not in clinical outcomes for infertile men with AZF microdeletion of the Y chromosome. Zygote (Cambridge, England) 23(5): 771-7	- Data cannot be extracted
Zhu, Yuanchang, Wu, Tonghua, Li, Guangui et al. (2015) The sperm quality and clinical outcomes were not affected by sY152 deletion in Y chromosome for oligozoospermia or azoospermia men after ICSI treatment. Gene 573(2): 233-8	- Outcome not in PICO *Surgical sperm retrieval rate not reported*

AZF: azoospermia factor

Excluded economic studies

No health economic search was conducted for this review question as it was a prognostic review, therefore no health economic evidence was excluded.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the predictive value of Y chromosome microdeletions (positive AZF a, b and c) for successful sperm retrieval in people with non-obstructive azoospermia or severe oligozoospermia?

No research recommendations were made for this review question.