Flannigan R, et al. 2023 Canadian Urological Association guideline: Evaluation and management of azoospermia

APPENDIX

Appendix 1. Needs assessment survey.

CUA Guideline on Azoospermia: Needs assessment/semi-structured interview

CUA Guideline Committee Member:_____

Interviewee Demographics:

	Interviewee #1	Interviewee #2
Practice Location		
Practice type (acad/comm)		
Years in practice		
Do you currently see outpatient consults for Infertility?		
Do you perform sperm retrievals?		
Do you perform vasectomy reversals?		
Do you refer your patients with azoospermia to another urologist who specializes in infertility		
Do you perform investigations of azoospermic men? If so which do you order?		

How would you describe your current level of comfort in treating men with azoospermia? (Rate 1-5, with 1=very uncomfortable, 5=very comfortable)		

Interview Questions:

1. Have you made use of existing clinical practice guidelines on infertility (CUA, AUA, EAU, ASRM etc)? If so, how helpful have these been in guiding your clinical care? Any comments?

Interviewee 1:

Interviewee 2:

2. Within your current scope of practice as it relates to management of azoospermia, what are some topic areas where you would like to have more information and guidance (ie gaps in your knowledge or skills)?

Interviewee 1:

Interviewee 2:

3. What topics would you like to see addressed in the new CUA guideline on azoospermia? (can provide prompts to interviewee with examples such as: role of the urologist in doing the initial lab evaluation etc, how to optimize hormone status, surgical sperm retrieval, surgical reconstruction techniques for vasal or epididymal obstruction, sperm retrieval for men lacking ejaculation and emission)

Interviewee 1:

Interviewee 2:

4. If the new CUA guideline provided evidence-based recommendations on aspects of azoospermia management that you do NOT currently perform (eg. hormone therapy to optimize non-obstructive azoospermia, surgical sperm retrieval, genetic investigations etc), do you think you would potentially expand the scope of your practice?

Interviewee 1:

Interviewee 2:

5. Any other comments/suggestions?

Appendix 2. Summary of judgements for cryopreservation of surgically retrieved sperm.

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

*Note: The intervention in this table is the use of fresh sperm, while the comparison is use of cryopreserved sperm.

Appendix 3. Summary of findings for cryopreservation of surgically retrieved sperm.

Summary of findings:

Sperm cryopreservation compared to fresh sperm in men with non-obstructive azoospermia

Patient or population: men with non-obstructive azoospermia
Setting:
Intervention: sperm cryopreservation
Comparison: fresh sperm

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with fresh sperm	**Risk with sperm cryopreservation**				
Clinical pregnancy	383 per 1,000	**345 per 1,000** (307 to 387)	**RR 0.90** (0.80 to 1.01)	2084 (22 observational studies)	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of sperm cryopreservation on clinical pregnancy. In every 1000 NOA couples who use cryopreserved sperm compared to fresh sperm, 38 fewer (95% CI from 76 fewer to 4 more) couples have clinical pregnancies.
Live birth	339 per 1,000	**261 per 1,000** (227 to 302)	**RR 0.77** (0.67 to 0.89)	1973 (21 observational studies)	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of sperm cryopreservation on live birth. In every 1000 NOA couples who use cryopreserved sperm compared to fresh sperm, 78 fewer (95% CI from 112 fewer to 37 fewer) couples have live birth.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

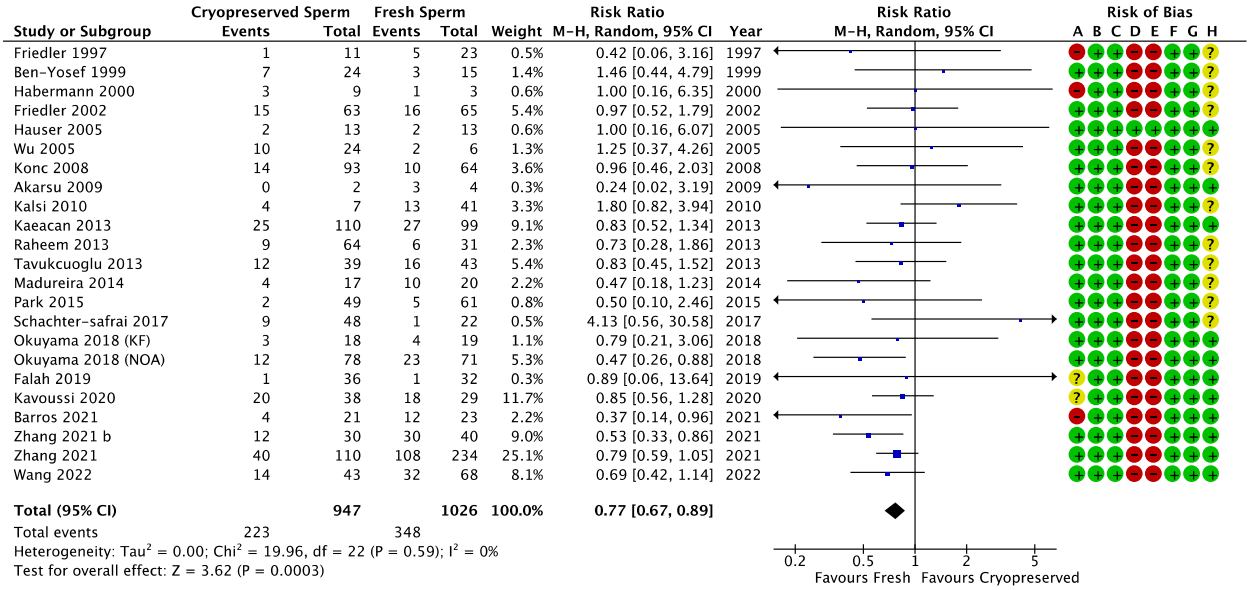
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

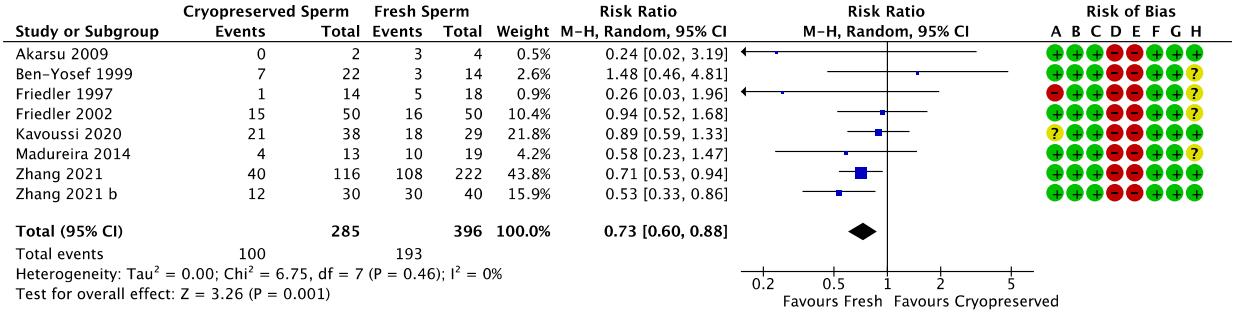
a. Studies are at high risk of bias, mainly for a lack of confounder measurement and adjustment.
b. As the individual study results vary considerably with very wide confidence intervals, we decided to rate down by one level for inconsistency and imprecision.
c. Based on the review of the funnel plot, the chances of publication bias are suspected.

Appendix 4A. Forest plot of adjuvant cryopreservation on live birth rates.



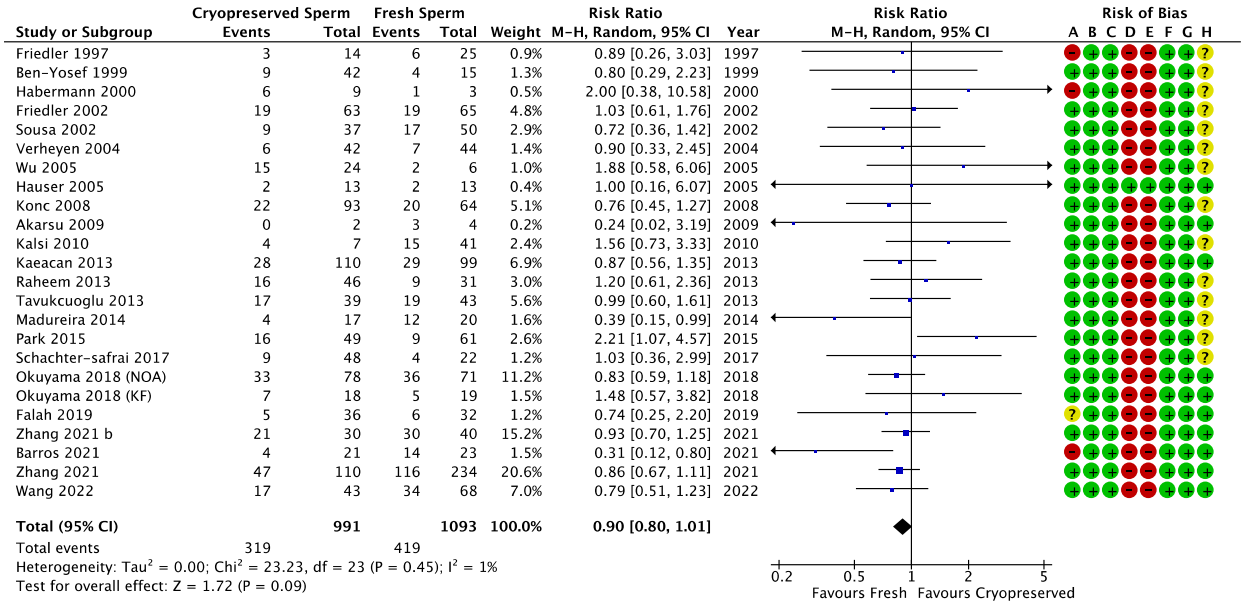
Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 4B. Forest plot demonstrating a sensitivity analysis of adjuvant cryopreservation on live birth rates among studies using an intention-to-treat-like methodology.



Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 5A. Forest plot of adjuvant cryopreservation on clinical pregnancy rates.



Study or Subgroup	Cryopreserved Sperm Events	Total	Fresh Sperm Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Friedler 1997	3	14	6	25	0.9%	0.89 [0.26, 3.03]	1997
Ben-Yosef 1999	9	42	4	15	1.3%	0.80 [0.29, 2.23]	1999
Habermann 2000	6	9	1	3	0.5%	2.00 [0.38, 10.58]	2000
Friedler 2002	19	63	19	65	4.8%	1.03 [0.61, 1.76]	2002
Sousa 2002	9	37	17	50	2.9%	0.72 [0.36, 1.42]	2002
Verheyen 2004	6	42	7	44	1.4%	0.90 [0.33, 2.45]	2004
Wu 2005	15	24	2	6	1.0%	1.88 [0.58, 6.06]	2005
Hauser 2005	2	13	2	13	0.4%	1.00 [0.16, 6.07]	2005
Konc 2008	22	93	20	64	5.1%	0.76 [0.45, 1.27]	2008
Akarsu 2009	0	2	3	4	0.2%	0.24 [0.02, 3.19]	2009
Kalsi 2010	4	7	15	41	2.4%	1.56 [0.73, 3.33]	2010
Kaeacan 2013	28	110	29	99	6.9%	0.87 [0.56, 1.35]	2013
Raheem 2013	16	46	9	31	3.0%	1.20 [0.61, 2.36]	2013
Tavukcuoglu 2013	17	39	19	43	5.6%	0.99 [0.60, 1.61]	2013
Madureira 2014	4	17	12	20	1.6%	0.39 [0.15, 0.99]	2014
Park 2015	16	49	9	61	2.6%	2.21 [1.07, 4.57]	2015
Schachter-safrai 2017	9	48	4	22	1.2%	1.03 [0.36, 2.99]	2017
Okuyama 2018 (NOA)	33	78	36	71	11.2%	0.83 [0.59, 1.18]	2018
Okuyama 2018 (KF)	7	18	5	19	1.5%	1.48 [0.57, 3.82]	2018
Falah 2019	5	36	6	32	1.2%	0.74 [0.25, 2.20]	2019
Zhang 2021 b	21	30	30	40	15.2%	0.93 [0.70, 1.25]	2021
Barros 2021	4	21	14	23	1.5%	0.31 [0.12, 0.80]	2021
Zhang 2021	47	110	116	234	20.6%	0.86 [0.67, 1.11]	2021
Wang 2022	17	43	34	68	7.0%	0.79 [0.51, 1.23]	2022
Total (95% CI)		**991**		**1093**	**100.0%**	**0.90 [0.80, 1.01]**	
Total events	319		419				

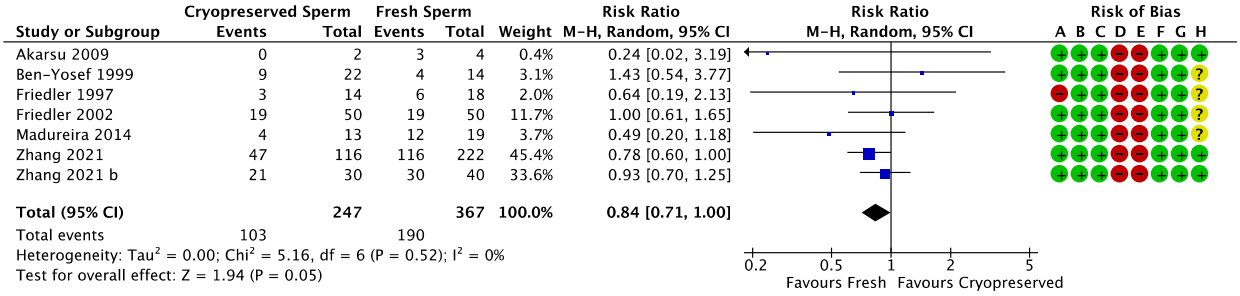
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 23.23$, df = 23 (P = 0.45); $I^2 = 1\%$
Test for overall effect: Z = 1.72 (P = 0.09)

Risk Ratio M-H, Random, 95% CI: 0.2, 0.5, 1, 2, 5 — Favours Fresh | Favours Cryopreserved

Risk of Bias: A B C D E F G H

Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 5B. Forest Plot demonstrating a sensitivity analysis of adjuvant cryopreservation on clinical pregnancy rates among studies using an intention-to-treat-like methodology.



Study or Subgroup	Cryopreserved Sperm Events	Total	Fresh Sperm Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Akarsu 2009	0	2	3	4	0.4%	0.24 [0.02, 3.19]
Ben-Yosef 1999	9	22	4	14	3.1%	1.43 [0.54, 3.77]
Friedler 1997	3	14	6	18	2.0%	0.64 [0.19, 2.13]
Friedler 2002	19	50	19	50	11.7%	1.00 [0.61, 1.65]
Madureira 2014	4	13	12	19	3.7%	0.49 [0.20, 1.18]
Zhang 2021	47	116	116	222	45.4%	0.78 [0.60, 1.00]
Zhang 2021 b	21	30	30	40	33.6%	0.93 [0.70, 1.25]
Total (95% CI)		**247**		**367**	**100.0%**	**0.84 [0.71, 1.00]**
Total events	103		190			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.16$, df = 6 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 1.94 (P = 0.05)

Risk Ratio M-H, Random, 95% CI: 0.2, 0.5, 1, 2, 5 — Favours Fresh | Favours Cryopreserved

Risk of Bias: A B C D E F G H

Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 6. Summary of judgements for neoadjuvant varicocele repair in NOA.

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Note: Intervention in this table represents performing a neo-adjuvant varicocele repair in NOA, while the comparison represents observation of the varicocele.

Appendix 7. Summary of findings for neoadjuvant varicocele repair in NOA.

Summary of findings:

Surgical varicocele repair compared to no varicocele repair in men with non-obstructive azoospermia and varicocele

Patient or population: men with non-obstructive azoospermia and varicocele
Setting:
Intervention: surgical varicocele repair
Comparison: no varicocele repair

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no varicocele repair	**Risk with surgical varicocele repair**				
Clinical pregnancy	95 per 1,000	**167 per 1,000** (40 to 692)	**RR 1.75** (0.42 to 7.27)	87 (1 observational study)	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of surgical varicocele repair on clinical pregnancy. In every 1000 NOA men who undergo varicocele repair, 72 more men (95% CI from 55 fewer to 597 more) have clinical pregnancy.
Live birth	95 per 1,000	**136 per 1,000** (32 to 582)	**RR 1.43** (0.34 to 6.11)	87 (1 observational study)	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of surgical varicocele repair on live birth rate. In every 1000 NOA men who undergo varicocele repair, 41 more men (95% CI from 63 fewer to 487 more) have Live birth.
Sperm retrieval	514 per 1,000	**612 per 1,000** (421 to 889)	**RR 1.19** (0.82 to 1.73)	260 (3 observational studies)	⨁◯◯◯ Very low[c,d]	The evidence is very uncertain about the effect of surgical varicocele repair on sperm retrieval. In every 1000 NOA men who undergo varicocele repair, 98 more men (95% CI from 93 fewer to 375 more) have sperm retreival.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

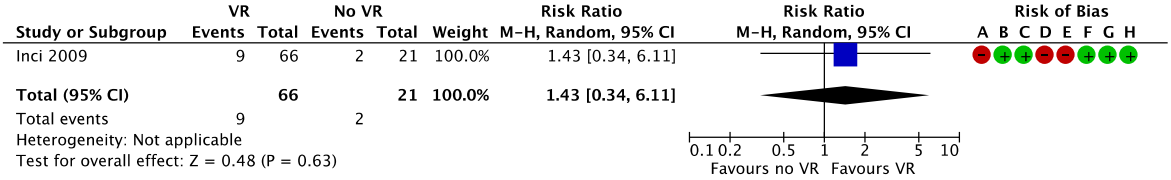
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

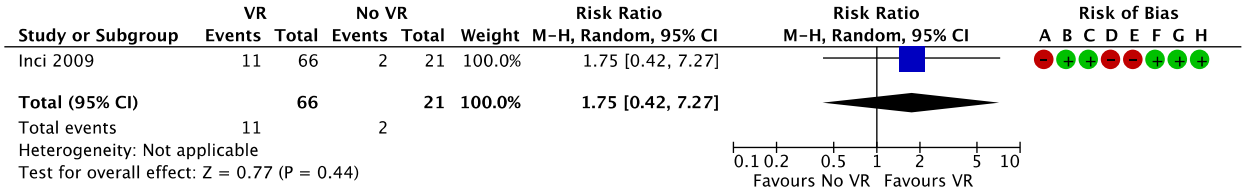
a. The only included study is at a high risk of bias.
b. Extremely few events and wide confidence interval.
c. None of the included studies is at low risk of bias.
d. Wide confidence interval with different boundary interpretations.

Appendix 8. Forest plot of neoadjuvant varicocele repair on live birth rate.



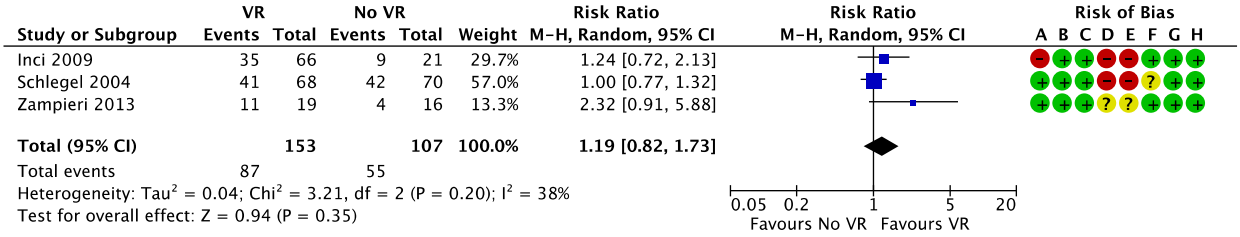
Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 9. Forest plot of neoadjuvant varicocele repair on clinical pregnancy rate.



Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 10. Forest plot of neoadjuvant varicocele repair on sperm retrieval rate.



Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 11. Summary of judgements for neoadjuvant hormone therapy in NOA.

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Note: Intervention in this table represents use of neo-adjuvant hormone therapy in NOA, where the comparison represents no treatment with respect to hormone therapy for the purpose of improving semen analysis parameters alone.

Appendix 12. Summary of findings for neoadjuvant hormone therapy in NOA.

Summary of findings:

Hormonal treatment compared to no hormonal treatment in men with non-obstructive azoospermia

Patient or population: men with non-obstructive azoospermia
Setting:
Intervention: hormonal treatment
Comparison: no hormonal treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no hormonal treatment	**Risk with hormonal treatment**				
Clinical pregnancy	224 per 1,000	**211 per 1,000** (128 to 343)	**RR 0.94** (0.57 to 1.53)	582 (3 observational studies)	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of hormonal treatment on clinical pregnancy.In the two observational studies that used hCG, FSH, a mixed approach to improve male infertility through hormonal treatments, 13 fewer couples (95% CI from 96 fewer to 119 more) had a clinical pregnancy in every 1000 men who received the treatment compared to no treatment.
Live birth rate	257 per 1,000	**193 per 1,000** (134 to 278)	**RR 0.75** (0.52 to 1.08)	615 (3 observational studies)	⨁◯◯◯ Very low[a,c]	The evidence is very uncertain about the effect of hormonal treatment on the live birth rate. In every 1000 NOA men who received hormonal treatment compared to no treatment, 64 fewer couples (95% CI from 123 fewer to 21 more) had a live birth.
Sperm retrieval	362 per 1,000	**506 per 1,000** (365 to 698)	**RR 1.40** (1.01 to 1.93)	1540 (11 observational studies)	⨁◯◯◯ Very low[a,c,d]	The evidence is very uncertain about the effect of hormonal treatment on sperm retrieval rate. In every 1000 NOA men who received hormonal treatment compared to no treatment, 144 more men (95% CI from 3 more to 336 more) had sperm retreival.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

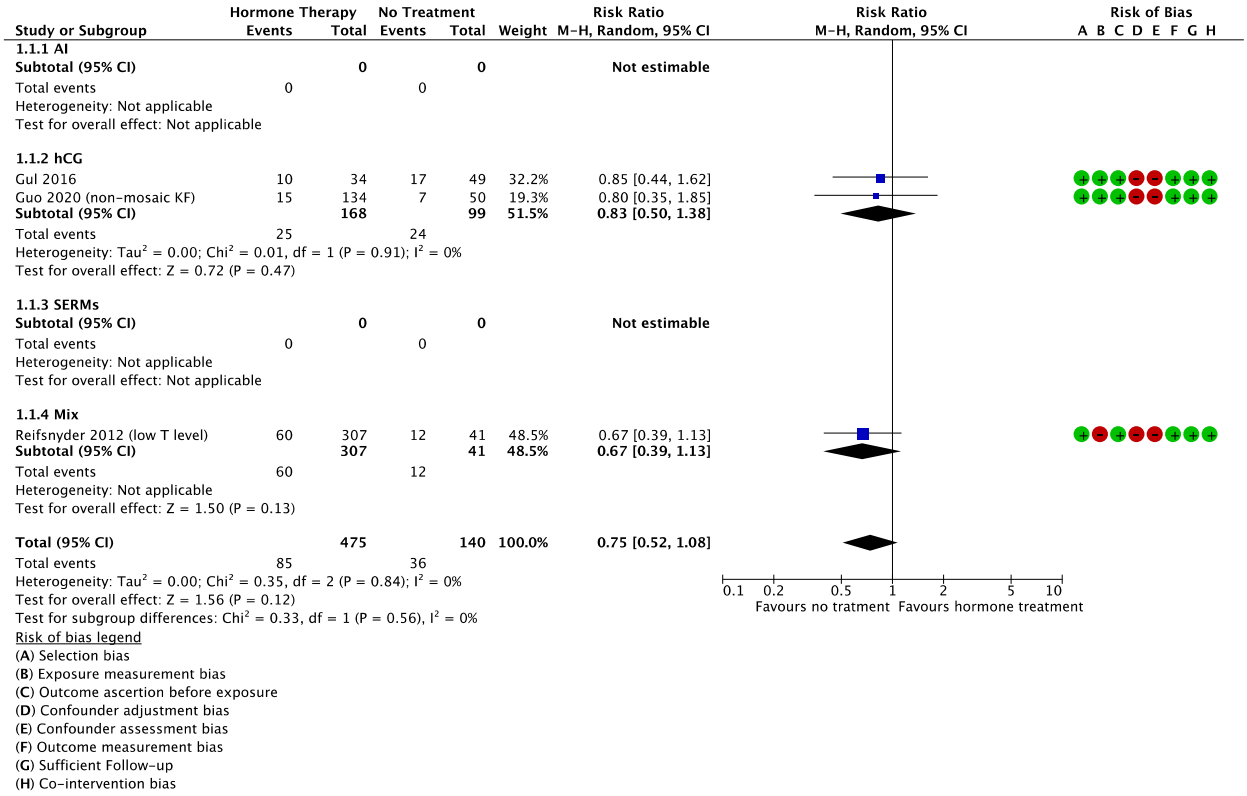
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

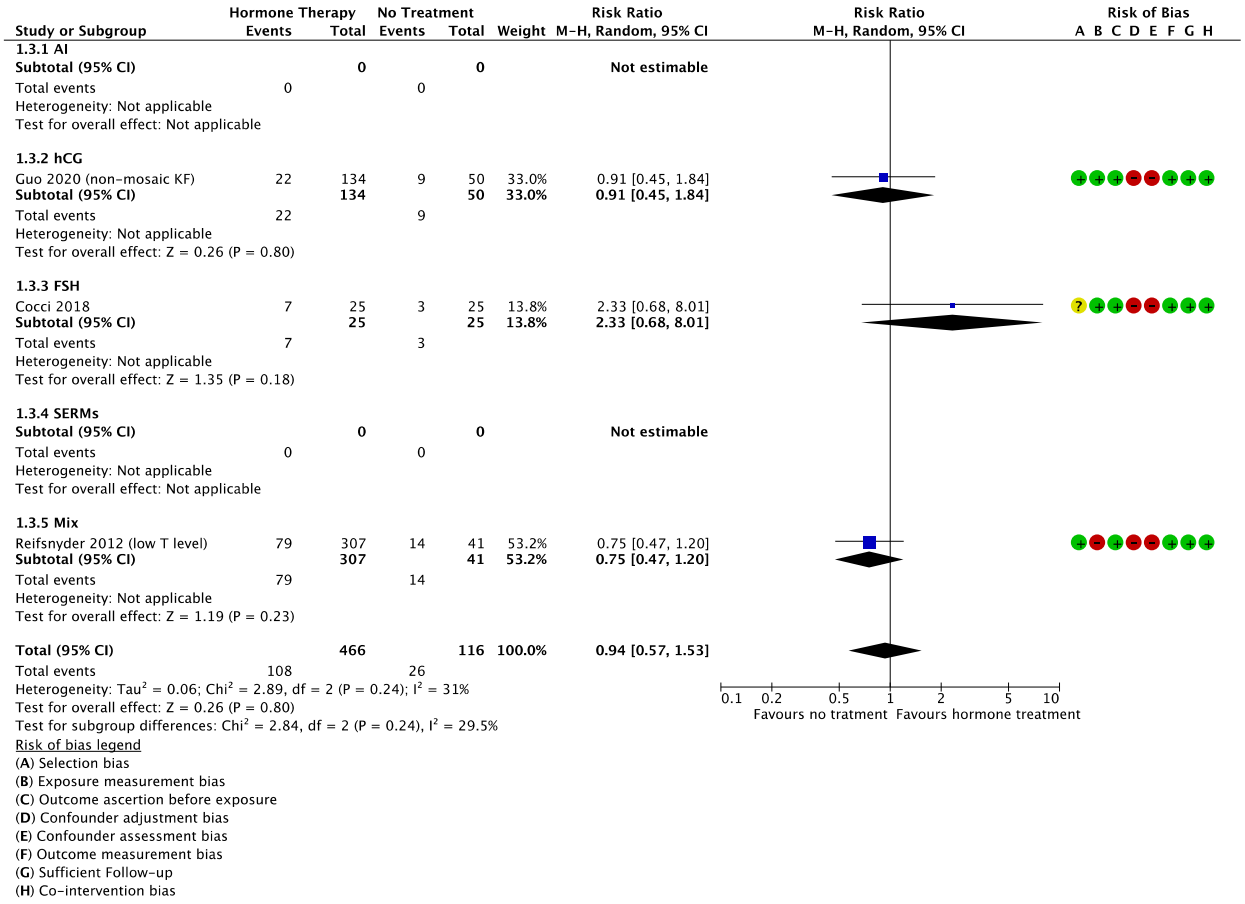
a. The studies included in the analysis are at high risk of bias especially because of lack of confounder measurement and adjustment.
b. Results of the study using FSH was considerably different from the other subgroups
c. The confidence interval of the absolute effect crosses the line of no impact and the boundaries fall into different interpretation zones.
d. Visual inspection of the confidence intervals demonstrates heterogeneity.

Appendix 13. Forest plot of neoadjuvant hormone therapy on live birth rates.



Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 14. Forest plot of neoadjuvant hormone therapy on clinical pregnancy rates.



Risk of bias legend
(**A**) Selection bias
(**B**) Exposure measurement bias
(**C**) Outcome ascertion before exposure
(**D**) Confounder adjustment bias
(**E**) Confounder assessment bias
(**F**) Outcome measurement bias
(**G**) Sufficient Follow-up
(**H**) Co-intervention bias

Appendix 15. Forest plot of neoadjuvant hormone therapy on sperm retrieval rates.