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Azoospermic Men with a History of Cryptorchidism Treated by Orchiopexy Have Favorable Outcomes after Testicular Sperm Extraction: A Systematic Review and Meta-Analysis

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Purpose: This systematic review and meta-analysis investigated the sperm retrieval rate (SRR) and pregnancy rate after testicular sperm extraction in men with azoospermia and those with a history of cryptorchidism treated by orchiopexy.

Materials and Methods: The SRR and clinical pregnancy rate were investigated. We performed a sub-analysis that included factors such as bilaterality, age, and idiopathic non-obstructive azoospermia (iNOA). The analysis comprised 13 studies from January 1995 to July 2021. The data sources were PubMed/MEDLINE, Embase, and the Cochrane Library included "cryptorchidism", "orchidopexy", "azoospermia", and "testicular sperm extraction".

Results: The overall mean SRR was 63.3% (95% confidence interval [CI], 57.6%–68.6%; I^2=62.4%), and the overall mean clinical pregnancy rate was 30.1% (95% CI, 22.6%–38.8%; I^2=69.9%). The meta-analysis comparing the SRR, there was no significant difference between patients with a history of bilateral and unilateral orchiopexy (relative risk [RR]=1.02; 95% CI, 0.89–1.16; p=0.79). Orchiopexy performed under the age of 10 years showed significantly increased SRR compared to the age of over 10 years (RR=1.25; 95% CI, 1.06–1.47; p=0.008). Azoospermic men with a history of cryptorchidism treated by orchiopexy had significantly higher SRR than iNOA (RR=1.90; 95% CI, 1.40–2.58; p<0.0001).

Conclusions: Men with azoospermia and a history of cryptorchidism treated by orchiopexy had significantly higher SRR than those with iNOA after testicular sperm extraction. Furthermore, patients who underwent orchiopexy before the age of ten years had significantly higher SRR than patients operated at an older than the age of ten years.

Keywords: Azoospermia; Cryptorchidism; Meta-analysis; Testicular sperm retrieval

INTRODUCTION

Cryptorchidism is a common genital anomaly in which one or both the testes fail to descend from the abdomen into the scrotum. The primary objective of performing orchiopexy in a cryptorchid patient is to

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reduce the risk of subfertility and testicular germ cell tumors [1,2]. From a histological perspective, cryptorchidism typically presents as decreased number of and reduced maturation of germ cells, resulting in impairment of maturated gonocytes with interstitial fibrosis [3-5]. Consequently, several studies have reported reduced fertility in men with a history of surgically treated cryptorchidism. Several studies have investigated the negative effects of cryptorchidism on testicular function, including parameters related to semen quality and reproductive hormones in adulthood [6,7]. Therefore, a history of cryptorchidism is known to compromise fertility, and the paternity rate significantly decreases in patients with a history of bilateral (67% *vs*. 93%) and unilateral cryptorchidism (55% *vs*. 86%) as compared to controls [8,9]. Approximately 10% of all infertile patients had a history of cryptorchidism [10], and the incidence of azoospermia in patients with bilateral cryptorchidism was reported to be approximately 46%. However, in patients with unilateral cryptorchidism, the incidence of azoospermia was significantly lower than bilateral cryptorchidism which reported 13% [11,12].

Non-obstructive azoospermia (NOA), which is defined as the absence of spermatozoa in the ejaculate secondary to impaired spermatogenesis within the testis, may have various etiologies, including cryptorchidism, varicocele, mumps orchitis, gonadotoxic medications, genetic abnormalities, chemotherapy/radiation, and other unknown causes currently classified as idiopathic [13]. In patients with NOA, the only well-proven solution for paternity is sperm retrieval by testicular sperm extraction (TESE), followed by *in vitro* fertilization with intracytoplasmic sperm injection.

Previous studies have suggested that the success rate of TESE in men with NOA and a history of cryptorchidism depends on predictive factors such as the age at orchiopexy, bilaterality, and total testicular volume [14-17]. However, robust data on TESE performed in patients with a history of cryptorchidism is still lacking due to smaller sample sizes and heterogeneity in studies. The aim of the present systematic review and meta-analysis was to analyze the sperm retrieval rate (SRR) and clinical pregnancy rate after TESE between patients with a history of orchiopexy and those with idiopathic NOA (iNOA), and to further investigate predictive factors through subgroup analysis.

MATERIALS AND METHODS

1. Evidence acquisition and registration

This systematic review and meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [18]. We registered the protocol prospectively in the PROSPERO database (CRD42020219235), and followed the guidelines of Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [19]. The detailed factors of Population, Intervention, Comparison, and Outcomes (PICO) are provided in Supplement Table 1.

2. Literature search

An extensive search of the literature published from January 1995 to July 2021 was performed using PubMed/MEDLINE, Embase, and the Cochrane Library. The search was conducted using the terms "cryptorchidism," "undescended testis," "orchidopexy," "azoospermia," and "testicular sperm extraction" without language restrictions. A full lists of search terms are listed in Supplement Table 2.

Two authors (D.K.K. and J.L.) independently screened the titles and main text of the articles to ensure that the study meets the inclusion criteria of this systematic review and meta-analysis. The disagreements were resolved through consensus with a third reviewer (T.H.L.).

3. Study selection

The inclusion criteria were as follows: 1) Reported SRR after TESE in men with azoospermia and a history of surgically treated cryptorchidism and 2) Reported clinical pregnancy rate after TESE in men with azoospermia and a history of surgically treated cryptorchidism. We excluded abstracts, case reports, animal studies, basic research studies, non-azoospermia studies, letters to the editor, review articles, systematic reviews, studies involving ≤10 participants, and studies that did not investigate the SRR. Fig. 1 depicts the flow diagram of the study selection.

4. Data collection

The following information was extracted independently by two trained investigators (D.K.K. and J.L.) by screening the titles and abstracts of the studies: 1) the date of publication, 2) study design, 3) number of participants, 4) country of investigation, 5) patient age,

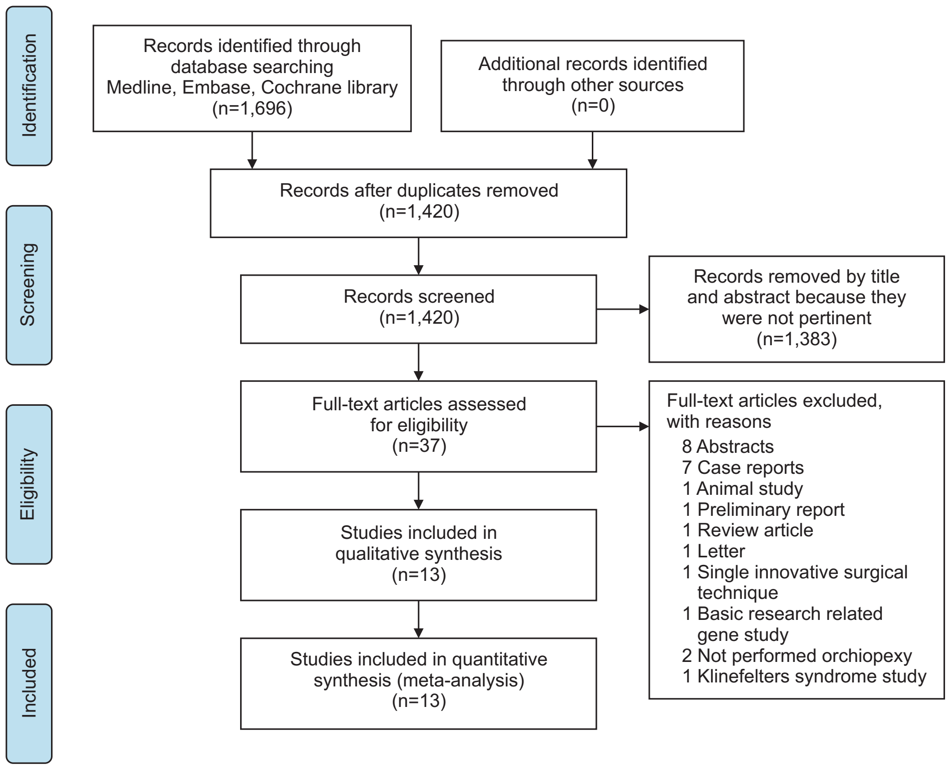

Fig. 1. Flow chart of the search and selection of literature included in the systematic review and meta-analysis.

6) testis volume, 7) follicle-stimulating hormone level, 8) SRR after TESE, 9) clinical pregnancy rate, and 10) sub-analysis of factors including bilateral *vs.* unilateral orchiopexy, operation age (age >10 y *vs.* ≤10 y; all included articles investigated in unified age of 10). The authors then reviewed the full text of the selected studies to assess eligibility.

5. Quality assessment

The quality of the studies included in the meta-analysis was determined using the quality assessment tool for before-after (pre-post) studies with no control group (available at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Considering the outcomes of this meta-analysis, question 4 (Were all eligible participants that met the pre-specified entry criteria enrolled?) was evaluated when a clear prospective study was adopted. Question 5 (Was the sample size sufficiently large to provide confidence in the findings?) was evaluated when the included study sample size calculation was clearly reported, or more than 100 participants were enrolled. Question 9 (Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?) was not applicable for the retrospective cohort studies. Question 12 (If the intervention was conducted at a group level [*e.g.*, a whole hospital, a community, *etc.*], did the statistical analysis take into account the use of individual-level data to determine effects at the group level?) was considered irrelevant for this systematic review and meta-analysis. The quality of each study or article was rated as good, fair, or poor.

6. Data extraction and statistical analysis

Event rate and relative risk (RR) were investigated using a fixed-effects model or random-effects model. The meta-analysis was performed using RevMan 5.3 (Cochrane Community, London, UK) and Comprehensive Meta-Analysis 3.0 (CMA; Biostat, Englewood, NJ, USA). All p-values were two-sided, and p<0.05 was considered statistically significant.

Forest plots were used to show the results of SRR and clinical pregnancy rate after performing an TESE. The relationship between the SRR and age, iNOA, and bilaterality was also investigated using forest plots.

A random-effects model was employed if high heterogeneity existed (I^2>50%).

RESULTS

1. Study characteristics

Fig. 1 shows the PRISMA flow chart of the studies

Table 1. Basic characteristics of studies included into systematic review

Author	Published year	Study design	Study country	Mean age (y) (mean±SD) (median, range)	FSH (IU/L) (mean±SD) (median, range)	Testicular volume (mL) (mean±SD) (median, range)	Number of participants (cryptorchidism) (iNOA)	Outcomes included in the article (SRR) (clinical pregnancy rate) (bilaterality) (age comparison) (ex-cryptorchid *vs.* iNOA)
Negri et al [15]	2003	Retrospective cohort	Italy	34.7±4.4	Ex-cryptorchid, 15.8±9.2 iNOA, 20.4±10.7	Ex-cryptorchid, 10.1±4.1 iNOA, 9.5±4.0	Bilateral Cryptorchidism, 30 iNOA, 107	SRR, 49.5% Ex-cryptorchid, 73%; iNOA, 40%
Raman and Schlegel [16]	2003	Retrospective cohort	USA	36.7±6.5	Ex-cryptorchid TESE success, 26.6±10.5 TESE fail, 31.5±15.7 iNOA TESE success, 22.4±16.8 TESE fail, 21.0±15.0	Ex-cryptorchid TESE success, 8.4±4.5 TESE fail, 6.3±3.4 iNOA TESE success, 9.9±5.1 TESE fail, 10.9±5.5	Cryptorchidism, 38 iNOA, 275	SRR Cryptorchidism, 74% iNOA, 58% Clinical pregnancy rate Cryptorchidism, 46% iNOA, 44%
Vernaeve et al [21]	2004	Retrospective cohort	Belgium	Orchidopexy, 34.0 NOA, 35.2	TESE success, 24.1 (17.9–30.3) TESE fail, 28.8 (19.4–38.2)	TESE success, 10 (8.3–11.9) TESE fail, 8.5 (5.9–11.1)	Cryptorchidism, 79 iNOA, 213	SRR Orchiopexy, 51.9% iNOA, 33.3% Clinical pregnancy rate Orchiopexy, 20.8% iNOA, 11.9%
Marcelli et al [23]	2005	Retrospective cohort	France	Bilateral, 31.34 (22–47) Unilateral, 30.88 (22–54)	FSH ≤10, n=38 FSH >10, n=104	Testicular volume ≥16, n=17 <16, n=125 10–15, n=26 6–10, n=73 0–5, n=26	Cryptorchidism, 142 (Bilateral, 87) (Unilateral, 55)	SRR Age <10 y, 71.8% SRR Bilateral, 63% Unilateral, 61.9%
Wiser et al [20]	2009	Retrospective cohort	Israel	Age ≤10 y, 33.7±5.2 Age >10 y, 33.1±6.8	Orchiopexy Age ≤10 y, 20.1±11.3 Age >10 y, 26.4±18.4	Orchiopexy Age ≤10 y: Right, 14.2±7.2 Left, 14.4±6.3 Age >10 y: Right, 14.2±7.5 Left, 13.6±7.0	Cryptorchidism, 42 Orchiopexy Age ≤10 y, 21 Age >10 y, 21	SRR Age ≤10 y, 61.9% Age >10 y, 67.1% Clinical pregnancy rate Age ≤10 y, 30.8% Age >10 y, 41.2%
Haimov-Kochman et al [24]	2010	Retrospective cohort	Israel	Ex-cryptorchid, 31.1±6.5 Non-cryptorchid, 32.7±7.7	Ex-cryptorchid, 30.7±25.4 iNOA, 17.9±14.8	Ex-cryptorchid, 10±6.5 iNOA, 11±5.5	Cryptorchidism, 15 (13 unilat, 2 bilat) iNOA, 142	SRR Ex-cryptorchid, 66%; iNOA, 47% Clinical pregnancy rate Ex-cryptorchid, 29%; iNOA, 41.3%
Zhang et al [25]	2017	Retrospective cohort	China	24–68 (34.6±5.3)	Overall, 28.3±8.8	Overall, 5.3±2.6	Cryptorchidism, 24 iNOA, 39	Ex-cryptorchid 66.6 (16/24); iNOA 20.5% (8/39)

Table 1. Continued 1

Author	Published year	Study design	Study country	Mean age (y) (mean±SD) (median, range)	FSH (IU/L) (mean±SD) (median, range)	Testicular volume (mL) (mean±SD) (median, range)	Number of participants (cryptorchidism) (iNOA)	Outcomes included in the article (SRR) (clinical pregnancy rate) (bialterality) (age comparison) (ex-cryptorchid *vs.* iNOA)
Barbotin et al [26]	2019	Retrospective cohort	France	Bilateral, 31 (25–42) Unilateral, 32 (24–43)	Cryptorchidism Bilateral, 21.3 (6.1–53.9) Unilateral, 19.3 (6.1–49.1)	Cryptorchidism Bilateral, 7.2 (2.8–14.4) Unilateral, 7.9 (3.6–16.5)	Cryptorchidism, 225 Bilateral, 145 Unilateral, 80	SRR Bilateral, 66.2% (96/145) Unilateral, 60.0% (48/80) Clinical pregnancy rate Bilateral, 17.4% (28/161) Unilateral, 27.8% (20/72)
Chen et al [22]	2019	Retrospective cohort	China	29.4±6.2	Ex-cryptorchid, 18.60±8.15 iNOA, 20.60±10.26	Ex-cryptorchid Right, 8.25±2.49 Left, 8.42±2.61 iNOA Right, 8.11±3.28 Left, 7.98±3.16	Cryptorchidism, 33 iNOA, 446	SRR Cryptorchidism, 84.8% (28/33) iNOA, 31.8% (142/446) Clinical pregnancy rate, 55.84%
Ozan et al [14]	2019	Retrospective cohort	Turkey	34.54±5.51	Total, 25.90±12.44 Unilateral, 22.71±11.86 Bilateral, 28.19±12.40 Orchiopexy Age ≤10 y, 24.83±12.06 Age >10 y, 27.25±12.87	Overall, 7.55±2.84 Unilateral: Right, 7.59±3.12 Left, 7.37±2.86 Bilateral: Right, 7.93±2.85 Left, 7.69±2.83 Orchiopexy Age ≤10 y: Right, 8.08±3.12 Left, 8.05±2.86 Age >10 y: Right, 7.42±2.72 Left, 6.90±2.70	Cryptorchidism,148 Unilateral, 62 Bilateral, 86 Orchiopexy Age ≤10 y, 83 Age >10 y, 65	SRR, 60.48% (90/148) Unilateral, 62.9% Bilateral, 59.3% Orchiopexy Age ≤10 y, 65.10% (54/83) Age >10 y, 55.4% (36/65) Clinical pregnancy rate, 28.4% (42/148) Unilateral, 29.03% (18/62) Bilateral, 27.9% (24/86) Orchiopexy Age ≤10 y, 32.5% (27/62) Age >10 y, 23.1% (15/86)
Li et al [27]	2020	Retrospective cohort	China	30.7±5.5	Overall, 19.4±18.9	Not available	Cryptorchidism, 20 Unilateral, 7 Bilateral, 13	SRR Unilateral, 85.7% Bilateral, 76.9% Age ≤10 y, 81.2% Age >10 y, 77.8%

Table 1. Continued 2

Author	Published year	Study design	Study country	Mean age (mean±SD) (median, range)	FSH (IU/L) (mean±SD) (median, range)	Testicular volume (mL) (mean±SD) (median, range)	Number of participants (cryptorchidism) (iNOA)	Outcomes included in the article (SRR) (clinical pregnancy rate) (bialterality) (age comparison) (ex-cryptorchid *vs.* iNOA)
Ortac et al [28]	2020	Retrospective cohort	Turkey	34.0±5.8	Overall, 22.2±14.4	Overall, 12.3±4.8	Cryptorchidism, 62 iNOA, 311 Unilateral, 15 Bilateral, 26 iNOA, 249	SRR Overall, 53.1% Orchiopexy (+), 51.2% Orchiopexy (-), 47.6%
Zhang et al [29]	2021	Retrospective cohort	China	31.3±3.4 30.9±5.1	Ex-cryptorchid, 24.59±12.73 iNOA, 20.55±10.86	Ex-cryptorchid, 8.49±3.43 iNOA, 8.13±3.97	Cryptorchidism, 52 iNOA, 319	SRR Ex-cryptorchid, 75% (39/59); iNOA, 30.7% (98/337) Clinical pregnancy rate Ex-cryptorchid, 53.9% (21/39); iNOA, 46.9% (45/96)

FSH: follicle-stimulating hormone, iNOA: idiopathic non-obstructive azoospermia, SRR: sperm retrieval rate, TESE: testicular sperm extraction.

according to their inclusion criteria in the metaanalysis. Basic characteristics of the included studies have been displayed in Table 1 [14-16, 20-29]. We identified a total of 1,696 articles, and after removing duplicates, we investigated the abstracts of 1,420 articles. We excluded 1,383 articles which were not pertinent for analysis. Thereafter, we assessed the full text of 37 articles to check for eligibility. Of these, 24 articles were excluded due to the following reasons: published with the abstract alone (8), case reports (7), animal study (1), reported a single innovative surgical technique (1), preliminary report (1), review article (1), letter to the editor (1), did not perform orchiopexy (2), Klinefelter syndrome research (1), and basic research related to genetics (1). Ultimately, we included 13 retrospective cohort studies as quantitative synthesis in the meta-analysis (Fig. 1, Table 1). The publication interval was from 2003 to 2021. The cohort sizes ranged from 15 to 225 patients. The studies were conducted in several countries including China (4), France (2), Israel (2), Turkey (2), the United States of America (1), Italy (1), and Belgium (1).

2. Meta-analysis outcomes

The overall mean SRR was 63.3% (95% confidence interval [CI], 57.6%–68.6%; I^2=62.4%) and the overall mean clinical pregnancy rate was 30.1% (95% CI, 22.6%–38.8%; I^2=69.9%) (Fig. 2, 3). The meta-analysis of patients with cryptorchidism who underwent orchiopexy revealed significantly higher SRR than iNOA (RR=1.90; 95% CI, 1.40–2.58; $p<0.0001$) (Fig. 4). SRR was significantly higher in patients who were surgically treated for cryptorchidism before the age of 10 years than in patients operated at an older age over 10 (RR=1.25; 95% CI, 1.06–1.47; $p=0.008$) (Fig. 5). However, there was no significant difference in SRR between patients with a history of bilateral and unilateral orchiopexy (RR=1.02; 95% CI, 0.89–1.16; $p=0.79$) (Fig. 6).

3. Quality assessment and qualitative risk of bias

Table 2 presents the quality assessment of the study methodology of each included study. The quality of each article was measured by the quality assessment tool for beforeafter (prepost) studies with no control group. Accordingly, seven, three, and three studies exhibited presented good, fair, and poor qualities, respectively. The common reasons for losing points in

Study name	Event rate	Lower limit	Upper limit	Z-value	p-value	Relative weight
Negri et al, 2003	0.495	0.402	0.589	−0.097	0.923	10.52
Raman and Schlegel, 2003	0.745	0.602	0.849	3.200	0.001	6.86
Vernaeve et al, 2004	0.519	0.410	0.627	0.337	0.736	9.60
Marcelli et al, 2005	0.521	0.439	0.602	0.503	0.615	11.26
Wiser et al, 2009	0.595	0.443	0.731	1.227	0.220	7.31
Zhang et al, 2017	0.667	0.461	0.824	1.601	0.109	5.07
Haimov-Kockman et al, 2010	0.667	0.406	0.854	1.266	0.206	3.65
Barbotin et al, 2019	0.640	0.575	0.700	4.143	<0.001	12.08
Ozan et al, 2019	0.608	0.527	0.683	2.609	0.009	11.24
Chen et al, 2019	0.848	0.684	0.935	3.548	<0.001	4.35
Li et al, 2020	0.800	0.572	0.923	2.480	0.013	3.54
Ortac et al, 2020	0.756	0.603	0.863	3.111	0.002	6.26
Zhang et al, 2021	0.661	0.532	0.770	2.428	0.015	8.26
Overall	0.633	0.576	0.686	4.502	<0.001	

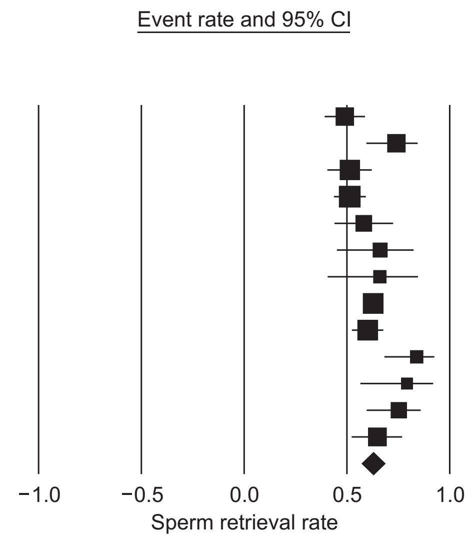

Fig. 2. Forest plot of overall sperm retrieval rate after testicular sperm extraction for men having a history of surgically treated cryptorchidism. CI: confidence interval.

Study name	Event rate	Lower limit	Upper limit	Z-value	p-value	Relative weight
Negri et al, 2003	0.333	0.190	0.516	−1.790	0.074	11.31
Vernaeve et al, 2004	0.172	0.098	0.284	−4.746	<0.001	12.80
Wiser et al, 2009	0.360	0.199	0.560	−1.381	0.167	10.58
Haimov-Kochman et al, 2010	0.290	0.159	0.470	−2.259	0.024	11.10
Ozan et al, 2019	0.284	0.217	0.362	−5.077	<0.001	17.10
Barbotin et al, 2019	0.206	0.159	0.263	−8.329	<0.001	17.65
Li et al, 2020	0.400	0.158	0.703	−0.628	0.530	6.37
Zhang et al, 2021	0.538	0.383	0.686	0.480	0.631	13.09
Overall	0.301	0.226	0.388	−4.265	<0.001	

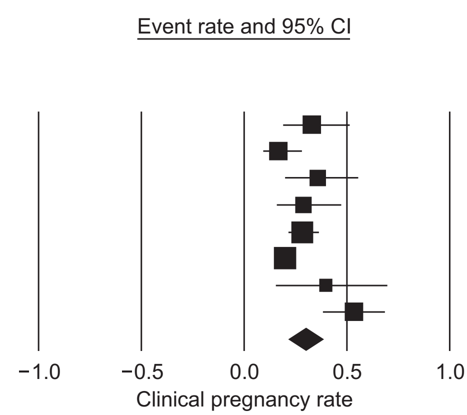

Fig. 3. Forest plot of the overall clinical pregnancy rate for men having a history of surgically treated cryptorchidism. CI: confidence interval.

Study or subgroup	Favours Ex-Cryporchid Events	Favours Ex-Cryporchid Total	Favours iNOA Events	Favours iNOA Total	Weight	Risk ratio M−H, random, 95% CI
Raman and Shlegel, 2003	35	47	160	274	19.7%	1.28 [1.05, 1.55]
Negri et al, 2003	22	30	31	77	16.8%	1.82 [1.29, 2.58]
Haimov-Kochman et al, 2010	10	15	67	142	15.7%	1.41 [0.95, 2.10]
Zhang et al, 2017	10	18	8	39	9.4%	2.71 [1.29, 5.69]
Chen et al, 2019	28	33	142	446	19.7%	2.66 [2.19, 3.25]
Zhang et al, 2021	39	59	98	337	18.8%	2.27 [1.77, 2.91]
Total (95% CI)		202		1,315	100.0%	1.90 [1.40, 2.58]
Total events	144		506			

Heterogeneity: $Tau^2=0.11$, $Chi^2=32.50$, df=5 (p<0.00001); $I^2=85\%$
Test for overall effect: Z=4.16 (p<0.0001)

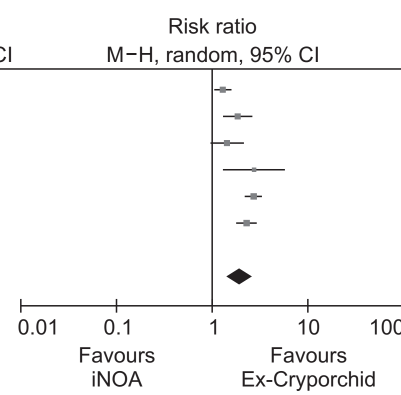

Fig. 4. Forest plot of the sperm retrieval rate for azoospermic men with a history of orchiopexy *versus* azoospermic men with idiopathic non-obstructive azoospermia (iNOA). CI: confidence interval.

the quality assessment were small sample size, poor description of the inclusion and exclusion criteria, and lack of precise statistical analysis. Both questions 4 and 9 were often considered "not applicable" since most of the studies involved a retrospective data analysis.

Sensitivity analysis was performed for the reliability

Study or subgroup	Orchiopexy age under 10 y Events	Orchiopexy age under 10 y Total	Orchiopexy age over 10 y Events	Orchiopexy age over 10 y Total	Weight	Risk ratio M−H, fixed, 95% CI
Raman and schlegel, 2003	16	17	7	16	7.2%	2.15 [1.22, 3.80]
Marcelli et al, 2005	8	9	9	11	8.0%	1.09 [0.76, 1.56]
Wiser et al, 2009	13	21	12	21	11.9%	1.08 [0.66, 1.79]
Ozan et al, 2019	54	83	36	65	40.1%	1.17 [0.90, 1.54]
Li et al, 2020	73	102	23	40	32.8%	1.24 [0.93, 1.67]
Total (95% CI)		232		153	100.0%	1.25 [1.06, 1.47]
Total events	164		87			

Heterogeneity: Chi^2=4.60, df=4 (p=0.33); I^2=13%
Test for overall effect: Z=2.67 (p=0.008)

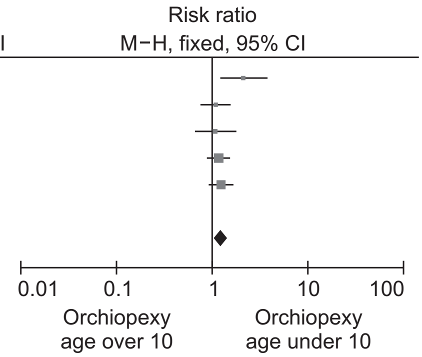

Fig. 5. Forest plot of the sperm retrieval rate comparison for orchiopexy at age under 10 years *versus* orchiopexy at age over 10 years. CI: confidence interval.

Study or subgroup	Bilateral Events	Bilateral Total	Unilateral Events	Unilateral Total	Weight	Risk ratio M−H, fixed, 95% CI
Marcelli et al, 2005	26	42	55	87	22.2%	0.98 [0.74, 1.30]
Barbotin et al, 2019	48	80	96	145	42.4%	0.91 [0.73, 1.12]
Ozan et al, 2019	39	62	51	86	26.5%	1.06 [0.82, 1.37]
Li et al, 2020	6	7	10	13	4.3%	1.11 [0.73, 1.70]
Ortac et al, 2020	11	15	10	26	4.5%	1.91 [1.07, 3.39]
Total (95% CI)		206		357	100.0%	1.02 [0.89, 1.16]
Total events	130		222			

Heterogeneity: Chi^2=6.07, df=4 (p=0.19); I^2=34%
Test for overall effect: Z=0.26 (p=0.79)

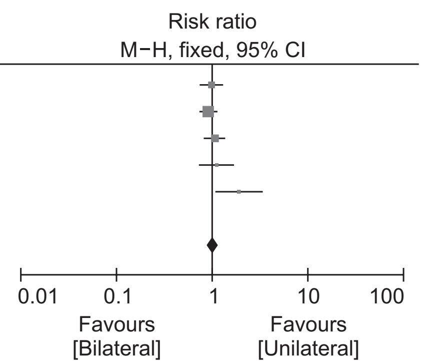

Fig. 6. Forest plot of the sperm retrieval rate for unilateral orchiopexy *versus* bilateral orchiopexy. CI: confidence interval.

of this meta-analysis, which estimated the influence of each article by removing each enrolled single study. An individual study affected SRR under 4.2% and clinical pregnancy rate under 4.1% (Table 3, 4). The combined results of our study were not significantly influenced by any individual data.

Funnel plots for the risk of publication bias revealed a certain degree of asymmetry (Fig. 7). Based on inspection of the plot, there was a certain degree of asymmetry, heterogeneity, and potential publication bias for SRR of overall analysis of the thirteen articles.

DISCUSSION

This is the first systematic review and meta-analysis on the SRR of cryptorchid patients who were treated with orchiopexy. We found that the overall SRR in patients with a history of cryptorchidism was 71.2%, which was significantly higher than that of iNOA patients (38.4%). Subgroup analyses suggested that orchiopexy performed at a younger age (≤10 y) could contribute to the improved SRR. However, our results revealed that there was no significant difference in SRR between patients with a history of bilateral and unilateral orchiopexy.

Many previous studies that investigated the association between cryptorchidism and fertility was based on limited clinical populations or small sample sizes, making it difficult to determine an accurate fertility status of cryptorchid patients. Furthermore, most of the data concerning fertility following cryptorchidism have reported only sperm parameters rather than factors related to paternity. One retrospective study revealed a paternity rate of 89.5% in men with unilateral cryptorchidism (10.5% infertile) compared with a rate of 94.6% in the control group (5.4% infertile), indicating a two-fold increased risk of infertility in unilateral cryptorchid patients [30]. A consequent study revealed that men with a history of bilateral cryptorchidism have a six-fold increased risk of infertility compared to a matched control group (38% *vs.* 6%) [31].

In regard to semen analysis, men with a history of bilateral cryptorchidism have reduced sperm quality compared to those with a history of unilateral crypt-

Table 2. Quality assessment of the included studies methodology according to the "quality quality assessment tool for before-after (pre-post) studies with no control group"

Quality assessment question	Negri et al, 2003 [15]	Raman and Schlegel, 2003 [16]	Vernaeve et al, 2004 [21]	Marcelli et al, 2005 [23]	Wiser et al, 2009 [20]	Haimov-Kochman et al, 2010 [24]	Zhang et al, 2017 [25]	Barbotin et al, 2019 [26]	Chen et al, 2019 [22]	Ozan et al, 2019 [14]	Li et al, 2020 [27]	Ortac et al, 2020 [28]	Zhang et al, 2021 [29]
Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No
Were all eligible participants that met the pre-specified entry criteria enrolled?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Was the sample size sufficiently large to provide confidence in the findings?	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No	No	No	No	No	No	No	No	No	No	No	No
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p-values for the pre-to-post changes?	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	No	No	No	No	No	No	No	No	No	No	No	No
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quality assessment	Good	Good	Good	Poor	Fair	Good	Fair	Good	Poor	Good	Poor	Good	Fair

NA: not applicable.

Table 3. Sensitivity analysis for sperm retrieval rate after TESE

Article	Author	Sperm retrieval rate	95% CI	Tau^2	I^2
Omitting	Negri et al, 2003 [15]	0.614	0.582–0.645	0.084	56.92%
Omitting	Raman et al, 2003 [16]	0.596	0.565–0.626	0.085	59.20%
Omitting	Vernaeve et al, 2004 [21]	0.609	0.577–0.639	0.097	61.30%
Omitting	Marcelli et al, 2005 [23]	0.615	0.582–0.646	0.094	58.60%
Omitting	Wiser et al, 2009 [20]	0.602	0.571–0.632	0.105	64.10%
Omitting	Zhang et al, 2017 [25]	0.600	0.569–0.630	0.100	63.63%
Omitting	Haimov-Kochman et al, 2010 [24]	0.601	0.570–0.631	0.100	63.82%
Omitting	Barbotin et al, 2019 [26]	0.591	0.557–0.625	0.116	62.12%
Omitting	Ozan et al, 2019 [14]	0.601	0.568–0.632	0.118	64.07%
Omitting	Chen et al, 2019 [22]	0.596	0.565–0.626	0.066	53.87%
Omitting	Li et al, 2020 [27]	0.599	0.568–0.628	0.087	60.47%
Omitting	Ortac et al, 2020 [28]	0.596	0.565–0.626	0.084	59.18%
Omitting	Zhang et al, 2021 [29]	0.598	0.567–0.629	0.102	63.10%
Pooled estimate		0.602	0.571–0.631	0.095	61.11%

TESE: testicular sperm extraction.

Table 4. Sensitivity analysis for clinical pregnancy rate after IVF-ICSI

Article	Author	Clinical pregnancy rate	95% CI	Tau^2	I^2
Omitting	Negri et al, 2003 [15]	0.298	0.217–0.395	0.220	73.53%
Omitting	Vernaeve et al, 2004 [21]	0.324	0.241–0.419	0.190	69.80%
Omitting	Wiser et al, 2009 [20]	0.295	0.216–0.390	0.211	73.03%
Omitting	Haimov-Kochman et al, 2010 [24]	0.304	0.221–0.402	0.226	74.16%
Omitting	Ozan et al, 2019 [14]	0.308	0.213–0.422	0.307	74.05%
Omitting	Barbotin et al, 2019 [26]	0.324	0.240–0.421	0.180	61.35%
Omitting	Li et al, 2020 [27]	0.295	0.218–0.386	0.182	73.27%
Omitting	Zhang et al, 2021 [29]	0.260	0.210–0.318	0.047	36.37%
Pooled estimate		0.301	0.226–0.388	0.195	69.92%

IVF: *in vitro* fertilization, ICSI: intracytoplasmic sperm injection.

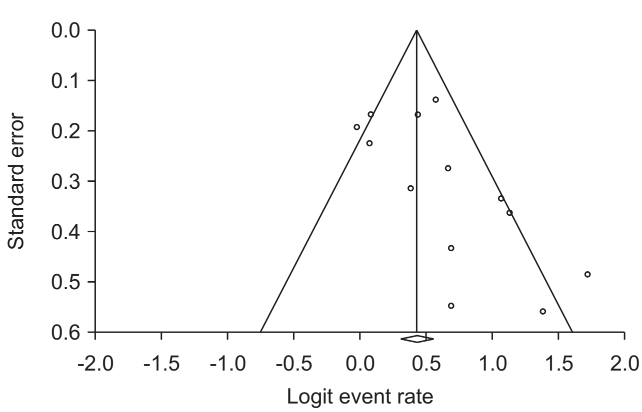

Fig. 7. Funnel plot for publication bias of cryptorchid azoospermia patients with a history of orchiopexy.

orchidism [32]. However, in our review, we included five studies in the sub-analysis which revealed that the unilateral cryptorchidism group did not show significantly higher SRR after TESE than the bilateral cryptorchidism group. In unilateral cryptorchid men, damaged germ cell function of the contralateral testis has been described previously, as germ cell hypertrophy compensates for the deficiency of an undescended testis [33]. Hadziselimovic and Herzog [34] reported that despite successful surgical correction of bilateral and unilateral cryptorchidism, 46.4% and 13% of patients developed azoospermia, respectively. van Brakel et al [9] reported that the normally descended testis in men with a history of unilateral cryptorchidism often had abnormal testicular consistency and lower testicular volume compared to that of the control group. These findings suggest that both testes are affected, even in unilateral cryptorchidism, which are in line with our results. A recent large population-based study also supported this finding, which did not detect a difference in testicular function between unilateral and bilateral cryptorchidism [7]. Considering these findings and the results of our meta-analysis that obtained an RR of 1.02 (p=0.79) while comparing the SRR in men with unilateral and bilateral cryptorchidism after TESE revealed that cryptorchidism could be regarded as a bilateral disease.

The correct age to perform orchiopexy for cryptorchid patients and whether SRR is influenced by the patients' age at the time of TESE remains controversial [16,20,21]. In this study, it was difficult to analyze whether the age at which TESE was performed affected the success of SRR. However, we analyzed the impact of the patient's age at orchiopexy by including five studies which unified an age of 10 years to compare the success of SRR; the SRR was higher in patients who underwent orchiopexy under the age of 10 years. Hadziselimovic and Herzog [34] revealed that a loss of germ cells begins at around six months of age in boys with undescended testes, and the number of adult dark spermatogonia begin to reduce in the first six months of age. Considering the arrest of gonocyte evolution that occurs in cryptorchidism by 6 to 8 months of age and the critical role of adult dark spermatogonia in fertility [35,36]. this testicular damage could progress in post-pubertal men. Therefore, gonadal dysfunction could be prevented by performing orchiopexy before the age of 10 years. Since the 1950s, the recommended optimal age of orchiopexy has been steadily declining, and it has been recently recommended to operate on cryptorchid males between the age of 6 to 12 months [37]. However, most included studies investigated the success rate of TESE according to the age at orchiopexy of 10 years of age, which may reflect the higher age recommended for orchiopexy in the past decades. The effect of early surgery that has been recently advocated should be re-evaluated when the children of the current generation grow up and their prognosis can be measured.

A previous study reported that an overall SRR of TESE for NOA patients was approximately 47% [38]. The etiology of NOA represents a heterogenous condition due to impaired spermatogenesis, including congenital causes such as Klinefelter's syndrome, cryptorchidism, and Y chromosome microdeletions, along with acquired causes of torsion, trauma, mumps orchitis, and iatrogenic problems (chemotherapy and radiotherapy). Furthermore, a significant proportion of NOA patients are categorized as idiopathic [22]. Therefore, the histopathology of testis can diversely present from hypospermatogenesis to Sertoli cell only (SCO). Owing to this heterogeneity, studies comparing the SRR in NOA patients based on the etiology are scarce. Several previous studies have shown that NOA caused by cryptorchidism has relatively higher SRR than other causes of NOA [16,39]. The present review examined six studies with this condition, and all studies demonstrated a higher SRR in NOA patients with a history of cryptorchidism than in patients with iNOA. The reason for a higher SRR in patients with a history of cryptorchidism might be attributed to the differences in testicular histopathology. The rate of SCO or complete maturation arrest was found to be 33.3% in patients with a history of undescended testes, which was lower than that of other causes (62.3%) [15]. Potential obstruction following orchiopexy and a high incidence of epididymal anomalies found in cryptorchid men could also explain our results [40].

Our systematic review and meta-analysis had several limitations. All studies in the meta-analysis were retrospective and observational in nature, and some studies included a low absolute number of patients with cryptorchidism. Prospective studies on cryptorchid azoospermia patients ongoing for several decades are hard to follow-up. The detailed techniques of TESE and different laboratory handling techniques varied with each study leading to heterogeneity in the analyzed parameters. There was certain degree of heterogeneity, potential publication bias for SRR of this meta-analysis. Another limitation was the heterogeneous definition of clinical pregnancy. The studies that were included did not clearly define clinical pregnancy, such as that based on serum human chorionic gonadotropin elevation or presence of gestational sac, and possible female factors, such as age, also have an impact on pregnancy outcomes. However, this systematic review and meta-analysis has a clinical significance as it states that cryptorchid azoospermia is a favorable prognostic factor for the success of TESE and has evidence for active treatment of TESE in cryptorchid azoospermia patients who underwent orchiopexy. Further long-term prospective studies are necessary for high grade evidence.

This meta-analysis found that azoospermia patients who underwent orchiopexy for cryptorchidism showed significantly higher SRR than those with iNOA after TESE. Further, patients who underwent orchiopexy at age under 10 years had significantly higher SRR. However, there was no significant difference in SRR between cases with a history of bilateral and unilateral orchiopexy Therefore, azoospermia in men with a history of cryptorchidism is a favorable prognostic factor for the success of TESE and has a clinical significance in TESE for azoospermia patients with cryptorchidism who underwent orchiopexy, regardless of bilateral and unilateral cryptorchidism.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: SWK. Data curation: JL, THL. Formal analysis: THL, DKK. Investigation: SHS. Methodology: DKK. Project administration: SWK. Resources: THL, DSK. Software: THL, DKK. Supervision: DSK, SHS. Validation: DSK, SHS. Visualization: JL. Writing – original draft: SWK, DKK. Writing – review & editing: SWK, DKK.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.210198.

REFERENCES

1. Chung JM, Lee SD. Individualized treatment guidelines for postpubertal cryptorchidism. World J Mens Health 2015;33:161-6.
2. Ryang SH, Jung JH, Eom M, Song JM, Chung HC, Chae Y, et al. The incidence and histological characteristics of intratubular germ cell neoplasia in postpubertal cryptorchid testis. Korean J Urol 2015;56:515-8.
3. Nistal M, Abaurrea MA, Paniagua R. Morphological and histometric study on the human Sertoli cell from birth to the onset of puberty. J Anat 1982;134(Pt 2):351-63.
4. Huff DS, Fenig DM, Canning DA, Carr MG, Zderic SA, Snyder HM 3rd. Abnormal germ cell development in cryptorchidism. Horm Res 2001;55:11-7.
5. Hadziselimović F, Seguchi H. [Electron microscopic study of the undescended testicles of children]. Acta Anat (Basel) 1973;86:474-83. German.
6. Trsinar B, Muravec UR. Fertility potential after unilateral and bilateral orchidopexy for cryptorchidism. World J Urol 2009;27:513-9.
7. Koch T, Hansen AH, Priskorn L, Petersen JH, Carlsen E, Main KM, et al. A history of cryptorchidism is associated with impaired testicular function in early adulthood: a cross-sectional study of 6376 men from the general population. Hum Reprod 2020;35:1765-80.
8. Lee PA, Coughlin MT. Fertility after bilateral cryptorchidism. Evaluation by paternity, hormone, and semen data. Horm Res 2001;55:28-32.
9. van Brakel J, Kranse R, de Muinck Keizer-Schrama SM, Hendriks AE, de Jong FH, Bangma CH, et al. Fertility potential in men with a history of congenital undescended testes: a long-term follow-up study. Andrology 2013;1:100-8.
10. Mieusset R, Bujan L, Massat G, Mansat A, Pontonnier F. Clinical and biological characteristics of infertile men with a history of cryptorchidism. Hum Reprod 1995;10:613-9.
11. Foresta C, Ferlin A, Garolla A, Milani C, Oliva G, Rossato M. Functional and cytologic features of the contralateral testis in cryptorchidism. Fertil Steril 1996;66:624-9.
12. Chung E, Brock GB. Cryptorchidism and its impact on male fertility: a state of art review of current literature. Can Urol Assoc J 2011;5:210-4.
13. Cocuzza M, Alvarenga C, Pagani R. The epidemiology and etiology of azoospermia. Clinics (Sao Paulo) 2013;68 (Suppl 1):15-26.
14. Ozan T, Karakeci A, Kaplancan T, Pirincci N, Firdolas F, Orhan I. Are predictive factors in sperm retrieval and pregnancy rates present in nonobstructive azoospermia patients by microdissection testicular sperm extraction on testicle with a history of orchidopexy operation? Andrologia 2019;51:e13430.
15. Negri L, Albani E, DiRocco M, Morreale G, Novara P, Levi-Setti PE. Testicular sperm extraction in azoospermic men submitted to bilateral orchidopexy. Hum Reprod 2003;18:2534-9.
16. Raman JD, Schlegel PN. Testicular sperm extraction with intracytoplasmic sperm injection is successful for the treatment of nonobstructive azoospermia associated with cryptorchidism. J Urol 2003;170(4 Pt 1):1287-90.
17. Çayan S, Orhan İ, Altay B, Aşcı R, Akbay E, Ayas B, et al. Fer-

tility outcomes and predictors for successful sperm retrieval and pregnancy in 327 azoospermic men with a history of cryptorchidism who underwent microdissection testicular sperm extraction. Andrology 2021;9:253-9.
18. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-12.
19. Tu YK, Greenwood DC. Modern methods for epidemiology. Dordrecht: Springer; 2012;173-89.
20. Wiser A, Raviv G, Weissenberg R, Elizur SE, Levron J, Machtinger R, et al. Does age at orchidopexy impact on the results of testicular sperm extraction? Reprod Biomed Online 2009;19:778-83.
21. Vernaeve V, Krikilion A, Verheyen G, Van Steirteghem A, Devroey P, Tournaye H. Outcome of testicular sperm recovery and ICSI in patients with non-obstructive azoospermia with a history of orchidopexy. Hum Reprod 2004;19:2307-12.
22. Chen X, Ma Y, Zou S, Wang S, Qiu J, Xiao Q, et al. Comparison and outcomes of nonobstructive azoospermia patients with different etiology undergoing MicroTESE and ICSI treatments. Transl Androl Urol 2019;8:366-73.
23. Marcelli F, Mahe P, Soulez B, Herbaut JC, Hermand E, Rigot JM. [Testicular sperm extraction in 50 men with nonobstructive azoospermia associated with cryptorchidism: Clinical parameters predictive of successful sperm extraction]. Andrologie 2005;15:19-23. French.
24. Haimov-Kochman R, Prus D, Farchat M, Bdolah Y, Hurwitz A. Reproductive outcome of men with azoospermia due to cryptorchidism using assisted techniques. Int J Androl 2010;33:e139-43.
25. Zhang J, Liu GH, Zhao LG, Liang XY, Wang ZY. [Microdissection testicular sperm extraction for patients with nonobstructive azoospermia: a report of 196 cases]. Zhonghua Nan Ke Xue 2017;23:804-7. Chinese.
26. Barbotin AL, Dauvergne A, Dumont A, Ramdane N, Mitchell V, Rigot JM, et al. Bilateral versus unilateral cryptorchidism in nonobstructive azoospermia: testicular sperm extraction outcomes. Asian J Androl 2019;21:445-51.
27. Li P, Yao CC, Zhi EL, Xu Y, Wan Z, Jiang YC, et al. Modified stepwise mini-incision microdissection testicular sperm extraction: a useful technique for patients with a history of orchidopexy affected by non-obstructive azoospermia. J Zhejiang Univ Sci B 2020;21:87-92.
28. Ortac M, Cilesiz NC, Demirelli E, Aydin R, Savun M, Ermec B, et al. Undescended testis does not affect the outcome of microdissection testicular sperm extraction. Urology 2020;141:77-81.
29. Zhang HL, Zhao LM, Mao JM, Liu DF, Tang WH, Lin HC, et al. Sperm retrieval rates and clinical outcomes for patients with different causes of azoospermia who undergo microdissection testicular sperm extraction-intracytoplasmic sperm injection. Asian J Androl 2021;23:59-63.
30. Lee PA, O'Leary LA, Songer NJ, Coughlin MT, Bellinger MF, LaPorte RE. Paternity after unilateral cryptorchidism: a controlled study. Pediatrics 1996;98(4 Pt 1):676-9.
31. Lee PA, O'Leary LA, Songer NJ, Coughlin MT, Bellinger MF, LaPorte RE. Paternity after bilateral cryptorchidism. A controlled study. Arch Pediatr Adolesc Med 1997;151:260-3.
32. Gracia J, Sánchez Zalabardo J, Sánchez García J, García C, Ferrández A. Clinical, physical, sperm and hormonal data in 251 adults operated on for cryptorchidism in childhood. BJU Int 2000;85:1100-3.
33. Koff SA. Does compensatory testicular enlargement predict monorchism? J Urol 1991;146(2 Pt 2):632-3.
34. Hadziselimovic F, Herzog B. Importance of early postnatal germ cell maturation for fertility of cryptorchid males. Horm Res 2001;55:6-10.
35. Rogers E, Teahan S, Gallagher H, Butler MR, Grainger R, McDermott TE, et al. The role of orchiectomy in the management of postpubertal cryptorchidism. J Urol 1998;159:851-4.
36. Hadziselimovic F. On the descent of the epididymo-testicular unit, cryptorchidism, and prevention of infertility. Basic Clin Androl 2017;27:21.
37. Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY, et al.; American Urological Assocation. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014;192:337-45.
38. Corona G, Minhas S, Giwercman A, Bettocchi C, Dinkelman-Smit M, Dohle G, et al. Sperm recovery and ICSI outcomes in men with non-obstructive azoospermia: a systematic review and meta-analysis. Hum Reprod Update 2019;25:733-57.
39. Ramasamy R, Padilla WO, Osterberg EC, Srivastava A, Reifsnyder JE, Niederberger C, et al. A comparison of models for predicting sperm retrieval before microdissection testicular sperm extraction in men with nonobstructive azoospermia. J Urol 2013;189:638-42.
40. van Brakel J, Dohle GR, de Muinck Keizer-Schrama SM, Hazebroek FW. Different surgical findings in congenital and acquired undescended testes. BJU Int 2012;110(8 Pt B):E387-91.