The Hospital for Sick Children

Technology Assessment at Sick Kids (TASK)

SYSTEMATIC REVIEW ON ORCHIDOPEXY FOR THE CANADIAN PAEDIATRIC SURGICAL WAIT TIMES PROJECT

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1 METHODS

Systematic reviews were performed according to the methods described below. One reviewer verified the publication eligibility based on the abstract and the same reviewer confirmed the eligibility by a review of the full text.

1.1 Guidelines

The first step was to search for already existing guidelines on orchidopexy. Table 1 includes the sources, terms, and limits used in the search.

Table 1 Search strategy, guidelines

Database sources	Search terms (Boolean searches)	Limits
Pubmed, Embase, INAHTA database, Cochrane database, National Guideline Clearinghouse, AHRQ, Urology associations (Canada, US, Europe), ICES, American Academy of Pediatrics	Pubmed (MeSH and individual terms), EMBASE (exploded and individual terms) Consensus, guidelines, clinical protocols, health planning guidelines, consensus development conferences, "position statement", recommendation, cryptorchidism (undescended testis*), orchidopexy, orchiopexy Other databases and websites Orchidopexy, orchiopexy, cryptorchidism, undescended testis used in combination	No limits to language but only publications in English and French were reviewed No limits to date of publication Latest search: May 5, 2009

AHRQ = Agency for Healthcare Research and Quality; ICES = Institute for Clinical Evaluative Sciences ; INAHTA = International Network for Agencies on Health Technology Assessment

* Inclusion of the term non-scrotal testis in the search strategy did not yield any additional record.

1.2 Systematic reviews, meta-analyses, comparative or non-comparative studies

Systematic literature review for systematic reviews, meta-analyses, comparative or non-comparative studies were performed. Databases included in the systematic review were Pubmed, Embase, and Cochrane database. No limitations for dates of publications were applied unless

specified in specific searches(tables 2-4). Date of last publication provided for each specific search (tables 2 -4).

Publications on surgical treatment of cryptorchidism (orchidopexy) and medical treatment were included. Separate searches were performed for publications on the effect of orchidopexy on fertility and testicular cancer.

In case meta-analyses or systematic reviews were identified, only studies published after the search period covered by the systematic review or meta-analysis were included.

Inclusion criteria are listed below:

- Publications in humans
- ≥ 20 patients included (total number of patients in case there was more than one study arm)
- Publications that evaluated outcomes and complications of orchidopexy or medical treatment OR
- Publications that evaluated the effects of orchidopexy on fertility in adults or testicular cancer
- Publications in pediatric patients
- Publications where mean patient age was lower or equal to four years[a] since the results would be more relevant given the current recommendation of operating children with cryptorchidism before 2 years of age.
  Studies in which mean age was greater than four years but that included subgroup analysis in patients younger than four years old were included.
- Publications in English and French

Exclusion criteria for individual studies are listed below.

- Studies exclusively in Prader-Willi syndrome, prune-belly syndrome, or Klinefelter syndrome

[a] Systematic reviews and meta-analyses in pediatric patients were included, further age limits were not applied since these publications included studies in pediatric patients with different age ranges, including patients with ≤ 4 years of age.

- Studies exclusively on retractile testis, ascending testis (non-congenital), or recurrent cryptorchidism
- Studies exclusively on the diagnosis or exploration of cryptorchidism, without surgery results (for orchidopexy outcome studies)
- Studies that evaluated orchidopexy re-operations
- Studies in animals

In cases where more than one publication was available for a given cohort of patients, only most recent publication was included.

Tables 2-4 show the search strategies used and search-specific limits.

Table 2 Search strategy, orchidopexy and medical therapy outcomes

Database sources	Search terms (Boolean searches)	Limits
Outcomes of surgical treatment		
Pubmed, Embase, Cochrane database	Pubmed (MeSH and individual terms), EMBASE (exploded and individual terms) and Cochrane databases (individual terms) cryptorchidism (undescended testis), orchidopexy, orchiopexy, laparoscopy, Fowler-Stephens	Individual studies published from January 1st 2005 on since a systematic review on both palpable and non-palpable testis included studies up to 2004* Latest search: 13/MAY/2009
Outcomes of medical (hormone) therapy		
Pubmed, Embase, Cochrane database	Pubmed (MeSH and individual terms), EMBASE (exploded and individual terms) and Cochrane databases (individual terms) Gonadotropin releasing hormone or human chrionic gonadotropin or luteinizing hormone releasing hormone or hormonal treatment AND cryptorchidism (undescended testis)	RCTs published from June 1st 2003 on since the most recent meta-analysis covers the literature up to that date. Latest search: 05/MAY/2009

Table 3 Search strategy, effects of orchidopexy on fertility and malignancies

Database sources	Search terms (Boolean searches)	Limits
Effect of orchidopexy on fertility in adults		
Pubmed, Embase, Cochrane database	Pubmed (MeSH and individual terms), EMBASE (exploded and individual terms) and Cochrane databases (individual terms) Fertility or infertility, or subfertility or paternity or sperm count or sperm concentration or sperm motility or testosterone, or Ad spermatogonia or follicle-stimulating hormone, or inhibin B AND Orchidopexy or orchiopexy OR surgery and cryptorchidism	No limits for date of publication were applied Studies exclusively in infertile men excluded Only studies that evaluated fertility in adults were included, i.e., excludes studies that evaluated fertility immediately after the surgery. Latest search: 20/MAY/2009
Effect of orchidopexy on testicular cancer		
Pubmed, Embase, Cochrane database	Pubmed (MeSH and individual terms), EMBASE (exploded and individual terms) and Cochrane databases (individual terms) Testicular neoplasm or testicular cancer or seminoma or malignancy AND Orchidopexy or orchiopexy or cryptorchidism	Studies published from 01/01/2007 since a meta-analysis covers the literature up to that date Latest search: 15/MAY/2009

* Studies published in 2004 were verified against the studies included in the systematic review and no additional study was identified. A systematic review published in 2008 included studies published up to 2007, however, since only studies on non-palpable testis were included in this systematic review, the literature search for individual studies was extended to 2005.

Table 4 Search strategy, effects of orchidopexy on fertility and malignancies

Database sources	Search terms (Boolean searches)	Limits
Testicular histology according to age		
Pubmed	Pubmed (MeSH and individual terms), EMBASE (exploded and individual terms) and Cochrane databases (individual terms) Fertility or sperm count or sperm concentration, or Ad spermatogonia or sperm motility or germ cell AND Fertility and cryptorchidism and histology	No limits for date of publication were applied Studies that compared the changes in histology in different age groups including 0-2 years included. Latest search: 25/MAY/2009
Effect of orchidopexy on testicular cancer		
Pubmed	Pubmed (MeSH and individual terms), EMBASE (exploded and individual terms) and Cochrane databases (individual terms) non-palpable testis or impalpable testis or (cryptorchidism and impalpable) or abdominal testis or abdominal testes AND MRI or magnetic resonance imaging or ultrasound or diagnostic laparoscopy	Studies published from 01/01/2007 since a meta-analysis covers the literature up to that date Latest search: 25/MAY/2009

1.3 Data presentation

Results of eligible publications were summarized in evidence tables. Tables with both study characteristics and study results were prepared.

One of the systematic reviews (1995)[1] that evaluated the surgical outcomes of orchidopexy pooled the results of the study without weighing studies according to sample size. The pooled analysis was updated with the results of the meta-analyses, systematic reviews, and observational studies. A weighted average (inverse variance[2]) was used. By this method, results of studies with larger variance contribute with less weight to the pooled estimate. and 95%

confidence intervals were calculated according to the number of testes operated on and percentage of success in each individual study in order to provide a measure of sample imprecision. Pooling data from a large variety of studies with possible heterogeneity in study population and other factors that may affect the outcome such as the experience of the surgical team, length of follow-up for the assessment etc. may pose limitations to the interpretability of the findings. Nevertheless part of the variation in results of individual studies may be due to sample size and this may be partially addressed by performing a pooled analysis. Results of individual studies are also reported.

1.4 Study quality evaluation

Study quality evaluation was assessed according to the Jadad score[3] (RCTs) and according to the guidelines published by the National Health and Medical Research Council (NHMRC) of Australia[4] for systematic reviews, meta-analyses, and non-randomized controlled trials. In the absence of standardized quality evaluation scales for non-comparative studies, their characteristics were summarized as a means of providing information on potential limitations to the validity of results.

1.5 Quality of the Evidence

The level of evidence and grades of recommendation were assessed based on the criteria from the GRADE working group.[5,6]

The levels of evidence and grades of recommendations based on the criteria from the GRADE working group[6] are shown in tables 5 and 6.

Table 5 Levels of evidence

Levels of Evidence	Criteria
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews or RCTs, or RCTs with a low risk of bias
1- (minus)	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies Or High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2- (minus)	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, i.e., case-reports, case-series
4	Expert opinion

Source: GRADE Working Group[5,6]

RCT = randomized controlled trial

Table 6 Grades of recommendation

Grades of recommendation	Criteria
A	At least one meta-analysis, systematic review, or RCT rated 1++ and directly applicable to the target population Or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rates as 2++ directly applicable to the target population and demonstrating overall consistency of results Or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rates as 2+ directly applicable to the target population and demonstrating overall consistency of results Or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+

Source: GRADE Working Group[5,6]

RCT = randomized controlled trial

2 RESULTS

2.1 Results of the systematic review

Table 7 provides the studies identified through our systematic review

Table 7 Results of the systematic review

	Publications identified	Details of systematic literature search
Guidelines and consensus on orchidopexy	3 publications: Guidelines of the European Association of Urology[7] (2008) Nordic consensus[8] (2007) Guidelines from Switzerland[9] (2008)	Search yielded 104 results. 3 publications considered eligible
Outcomes of orchidopexy	3 systematic reviews[1,10,11] 6 Randomized or non-randomized controlled trials[12-17]	Search yielded 439 results 26 possibly eligible based on abstract review 14 publications were considered eligible based on full text article
Outcomes of the use of hormones before or after study orchidopexy	5 Randomized or non-randomized controlled trials[18-22]	
Hormone treatment of cryptorchidism (no surgery)	2 meta-analyses[23,24] 1 systematic review[25]	Search yielded 91 results 3 publications eligible No additional RCT was identified beyond the search period of systematic review and meta-analyses.
Orchidopexy effects on fertility	10 observational studies[26-35]	Search yielded 931 results 47 possibly eligible based on abstract review 10 publications considered eligible based on full text article
Testicular histology according to age	8 observational studies[16,36-42]	Search yielded 232 results 8 publications considered eligible
Orchidopexy effects on testicular cancer	2 meta-analyses[43,44] 1 systematic review[45] 3 cohort or case-control studies[46-48]	Search yielded 323 results 6 publications considered eligible
Diagnostic workup of impalpable testes	2 systematic reviews[49,50] 15 observational studies[49,51-64]	Search yielded 508 results 38 possibly eligible based on abstract review 17 publications considered eligible

2.2 Study results

2.2.1 Study results, studies on orchidopexy

Table 8 Study results, non-palpable testes, 2-stage Fowler-Stephens orchidopexy. Laparoscopy vs. Open surgery

Study (year) Period of operations	Methods	Definition of success	Technique	Interval between stages	Mean age	Characteristics	No. testes	Success rate (95% CI)*	Complications
Abolyosr[12] (2006) Operations:2001-2005	RCT F-up:9-31 mos	According to scrotal position and atrophy	1st step: laparoscopy 2nd step random. to laparoscopy (A) or orchidopexy (B)	6 mos	5.3 yrs (1-16)*	High intra-abdominal testes	41 A: 21 B: 20	41 (100%) satisfactory scrotal position	Atrophy§ A: 2 (9.5%) B: 3 (15%)

f-up = follow-up ; mos= months ; RCT= randomized controlled trial
* Mean age for entire cohort
§ Authors concluded that both techniques are fairly comparable but laparoscopy results in significantly less morbidity. Nevertheless authors preferred open surgery approach since it allows adequate visualization and mobilization of the testis and it also permits harvesting the testis with sufficient peritoneal flap during the second stage of the Fowler-Stephens technique without jeopardizing the vessel blood supply.

Table 9 Study results, non-palpable testes, laparoscopy vs. inguinal exploration followed by orchidopexy

Study	Methods	Definition of success	Patient age	Characteristics	No. testes	Success rate	Atrophy	Complications
Chandrasekharm[13] (2005) Procedures over 3.5 yr period	Case-control Age-matched controls	Scrotal position	3 yrs (10 mos-11 yrs)	Canalicular: 48% Low abd: 35% High abd: 18% Similar in 2 groups	27* Laparoscopy (A): 13 Inguinal: (B): 14	4-6 wks A: 11/13 (85%) vs. B: 12/14 (86%)	4-6 wks A: 2 (15%) vs. B: 2 (14%)	NR

abd = abdominal ; mos = months ; NR= not reported ; wks = weeks ; yr = year
*Originally 40 patients were included, however, non-viable testes on exploration, 13 (7 in laparoscopy and 6 in inguinal exploration groups) were removed and did not undergo orchidopexy, therefore not included in the analysis.

Table 10 Study results, non-palpable testes, direct laparoscopic orchidopexy vs. open orchidopexy

Study	Methods	Definition of success	Technique	No. testes	Mean age	Characteristics	Success rate	Atrophy	Complications
Abolyosr[12] (2006) Operations:2001-2005	RCT f-up:9-31 mos	According to scrotal position and atrophy	Randomized to laparoscopy (A) or open orchidopexy (B)	34 A: 18 B: 16	5.3 yrs (1-16)§	Low abdominal testes	34 (100%) satisfactory scrotal position in both groups	0	NR

f-up = follow-up ; mos = months ; NR = not reported ; RCT = randomized controlled trial ; yrs = years

Table 11 Study results, non-palpable testes, prescrotal orchidopexy vs. inguinal approach

Study	Study design	Definition of success	# testes	Mean age	Characteristics	Success rate	Complications	Atrophy	Re-operations
Al-Mandil[14] (2008) 2004-2007	Case-control* F-up: 6-42 mos	Complications	56 pts (A, prescrotal) 47 (B, inguinal)	4.7 yrs	Primary UDT Location External ring A: 26 (41%) B: 21 (40%) Canalicular right side: A: 30 (48%) B: 26 (55%)	NR	Re-ascent: A: 1 (1.6%) B: 1 (1.9%) Hernia: A: 2(3.2%)§ B: 0 Wound infection A: 1(1.6%) B: 1(1.9%)	0	1 (1.6%) vs. 1 (1.9%) successfully corrected by inguinal orchidopexy

f-up = follow-up ; mos = months ; NR = not reported ; yr = year
Age-matched controls who underwent inguinal approach orchidopexy performed by a different surgeon.
§ One week after the orchidopexy one patient presented with hernia that required emergency operation and bowel resection. The second patient presented with asymptomatic swelling at 8 months follow-u.

Table 12 Study results, palpable testes, open orchidopexy comparing different age groups

Study (year) Period of operations	Methods	Definition of success	# testes	Mean patient age	Characteristics	Success rate	Complications
Kollin[15] (2007) Operations started in 1998	RCT Surgery 9 mos (A) vs. at 3 yrs (B) F-up: 4 yrs	Position and volume (clinical and US exams) vs. normally descended testis	A: 72 B: 83	Surgery at 9 mos (A) or 3 years (B) of age	Unilateral (100%) Palpable (100%)	Testicular volume change A : 0.35 ml (6 mos), 0.50 (4yrs) p<.001 ¶¶ B: no significant growth before or after surgery	NR
Park[16] (2007) Operations: 1998-2001 1996-2005 (controls)	Retrospective Comparing different age groups: ≤1 yr, 1-2yrs, 2-4yrs, > 4yrs	Testicular volume Hystological parameters*, mean tubular diameter (MTD), sertoli cell index (SCI)	N=65	1.95 yrs (0.6-9) ≤1yr:20 (31%) 1-2yrs:30 (46%) >2yrs: 15 (23%)	Unilateral (100%) Inguinal position (100%)	Histological parameters*: ≤ 1yr: higher vs. >1yr (p<.001) Testicular volume, MTD, SCI – not statistically significantly different among age groups	NR
Michikawa[17] (2007) Operations: 1992-2001	Retrospective f-up: 5 yrs Subgroups: surgery before (A) or after (B) 2yrs	Testicular volume (ratio of contralateral testis) Atrophy Incidence risk of morphol abnorm¦	< 2 yrs (A) 13 testes > 2 yrs (B) 10 testes	A: 1.4 ± 0.2 B: 2.8 ± 0.7	Unilateral (100%) Intracanincular A: 10(77%) B: 10(100%) Intraabdominal A§: 1(7.7%) B: 0	Testicular volume A: 1.54±1.03 ml ; B: 1.82±1.09 IR Ratio (NS) A: 0.59 , B: 0.51 IR morphological abnormalities A: 2/8 (25%) , B: 5/6 (83%) p=0.05	NR

f-up = follow-up ; MTD = mean tubular diameter ; mos = months ; NR = not reported ; NS = not statistically significant ; RCT = randomized controlled trial ; SCI = sertolli cell index ; US = ultrasound ; vol = volume ; yr = year

¶ The authors concluded that orchidopexy at 9 months leads to a significant catch-up growth of the initially undescended testis up to age 4 years. In patients operated at age 3 years growth of testes could not be salvaged up to the latest follow-up of 4 years. Results suggest that surgery at 9 months is beneficial to testicular growth.

§ In addition, group A (surgery before 2 years of age) had 1 (7.7%)testis in the suprapubic location, and there was no information in 1 case.

¦ Morphological abnormalities defined as diffuse hypoechoic lesions within the internal testicular architecture, microlithiasis such as depiction of multiple small foci or high level echogenicity, an irregular surface, and atrophy or volume reduction.

*Mean tubular fertility index (MTFI) and germ cell count (GC)

¶¶Surgery at 9 months: significant partial catch-up growth based on volume

Comments Kollin et al.

- The study included a relatively large number of patients, 155 in total.
- The patients were randomized to undergo orchidopexy either at 9 months or 3 years of age.
- The outcome, testicular volume before and after surgery, showed a statistically significant increase in the 9-month group, but no difference in the 3-year group.
- Clinical significance of the difference in the 9-month group was not discussed.

Comments Park et al.

- Non randomized study comparing orchidopexy outcomes among different age groups. Also compares with retrospectively collected orchiectomy outcomes.
- Orchidopexy group included 65 patients. No mention to other patient characteristics that may impact the outcomes.
- Differences in histological findings, clinical importance not discussed.

Comments Michikawa et al.

- The analysis was based on a retrospective chart review. Two pediatric surgeons evaluated the images taken before surgery and 5 years after surgery in a blinded fashion.
- The two groups were very small, 13 and 10 patients, which makes it difficult to compare. According to the authors, five patients were lost to follow-up, resulting in a total sample of 18 patients. In addition, only 14 patients, 8 and 6 in groups A and B, respectively, were included in the morphological abnormalities analysis.
- It needs to be verified if the outcomes and differences between groups are clinically significant

Table 13 Study results, palpable testes, use of hormones before surgery

Study (year)	Study Methods	Definition of success	Hormone/dose	# patients	Mean age	Characteristics	Results	Atrophy	Complications
Jallouli[18] (2009)	RCT Type of orchidopexy not clear Measurements after surgery	Fertility index # complete tubules and Ad (dark) spermatogonia in periopertive biopsy Stratified by age (< 36 mos, > 36 mos)	1.2 mg GnRH daily intranasal for 4 weeks (A) vs. no hormone (B)	24 (12 each)	A: 38 months (21-110) B: 34.5 months (12-123)	Intracanicular testes (all patients) Unilateral undescended testes	Spermatogonia/ tubule A: 0.88 (SD 0.31) B: 0.49 (SD 0.52) P=0.002 Statistical significance only in >3 yrs (values not given) No recurrence of cryptorchidism in either group (f-up not reported)	B: 1(8%) atrophic seminiferous tubule	No side-effects in hormone treated group
Schwentner[19] (2005)	RCT Orchidopexy Measurements after surgery	Fertility index using specimen from biopsies taken during operation Stratified by age group	1.2 mg GnRH (A) daily intranasal for 4 weeks vs. no hormone (B) Surgery was done 4 weeks after end of hormone treatment	42 (63 testes) 21 each group	A: 32 mos (11-100) B: 47 mos(13-100)	Unilateral A: 12 (57%) B: 9 (43%	Spermatogonia/ tubule A: 1.05 (SD 0.71) B: 0.52 (SD0.39,) P=0.007 < 24 mos (p=.03)§ A: 1.27 (SD 0.98) B: 0.29 (SD 0.25) 25-72 mos A: 0.94 (SD 0.54) B: 0.56 (SD 0.42) > 73 mos A: 0.83 (SD 0.22)		NR

							B: 0.57 (SD 0.40)		
Hadziselimovic[22] (2005)	Case control	Number of Ad spermatogonia / tubular cross section (tbx)	1,500 IU HCG IM for 3wks (not clear if/when underwent surgery	65 patients 33 orchidopexy (A) 32 HCG (B)	NR	Unilateral (all)	> 0.1 Ad/tbx* A: 6 (18.2%) B: 17 (53.1%) P<.019)		

Ad/tbx = spermatogonia per tubular cross-section ; IU = international units ; GnRH = gonadotropin-releasing hormone ; HCG = human chorionic gonadotrophin ; IU = international units ; mos = months ; NR = not reported ; SD = standard deviation ; US = ultrasound
*Breakdown chosen as low normal range
§ Comparing patients operated before vs. after 2 years of age

Comments Jallouli et al.

- Stratified analyses showed no difference in fertility index between patients treated before or after 36 months of age in either group was noted. Authors mentioned that statistical significance was only seen in patients > 3 years old, these statement seems to be regarding the comparison between patients with and without hormone treatment.
- Results are statistically significant however clinical significance was not discussed by the authors.
- Length of follow-up is not clear, likely not enough to evaluate long-term effects.
- Small sample size, especially for stratified analyses.

Comments Schwentner et al.

- Location of undescended testes not provided - it may influence results
- Results are statistically significant however clinical significance was not discussed by the authors.
- Length of follow-up is not clear, likely not enough to evaluate long-term effects.
- Small sample size, especially for stratified analyses.
- Differences in fertility index between groups with unilateral undescended testes could not be investigated due to age difference. Difference was statistically different in bilateral undescended testes, 0.96 (SD 0.47) vs. 0.56 (SD 0.38) in hormone treated and untreated groups, respectively.

Comments Hadziselimovic et al.

- Poor methods description. It is not clear that patients in hormone group underwent surgery, when, and if it was the same technique as in the surgery only group.
- Patient characteristics and calendar time of treatment not provided. Not clear if groups are comparable. Patient age not provided. Location of testes not provided.
-

Table 14 Study results, palpable testes, use of hormones after surgery

Study	Study Methods	Definition of success	Hormone/dose	No. patients	Mean age	Characteristics	Results	Complications
Hadziselimovic[20] (2008) **Operations: NR** **Schoemakers orchidopexy**	Case-control	Testicular volume Spermiogram Measurement 15-19 yrs after surgery	LHRH buserelin 10µg (A) on alternate days for 6m intranasal 3m after surgery Control group (B) had surgery but no hormone therapy (comparable in age and germ cells measurement)	A: 15 B: 181	At surgery 3 yrs (1-6)	Location Inguinal / external inguinal ring A: 14 (93%)* B: 180 (99%)* After surgery all patients <0.2 germ cells/tubular cross section and 0 Ad (dark) spermatogonia	At 19 yrs of age Testicular volume A: 29ml (22-36) B: 38ml (30-46) in descended testis Spermiogram A: 13(87%) normal sperm concentration B: 15(100%) severe oligospermia	NR
Hadziselimovic[21] (1997) **Operations: NR** **Schoemakers orchidopexy**	Case-control	Sperm count and volume (spermiogram)	LHRH intranasal 10µg (A) every 2 days for 6m vs. surgery alone (B)	A: 10 B: 23	Surgery A:9.4±2.8 yrs Treatment A: 22.1±2.07 yrs B: 20.9±2.5 yrs	Scrotal position (all) Bilateral: 3 (30%) Control Bilateral:13 (57%) Both < 0.2	Extremely small number of germ cells/tbcx in both groups Sperm count/ejaculate 29.4 vs. 6.5 p<.003	NR

						spermatogonia /tbcx at biopsy HCG before surgery No testicular ascent	% normal sperm 31.6 vs. 15.2 p=.03 % motile sperm 41.3 vs. 11.2 (.001	

SD = standard deviation ; LHRH = luteinizing hormone releasing hormone ; NR = not reported ; US = ultrasound ; yrs = years
* Abdominal location in one patient in each group.

Table 15 Study results, non-palpable testes, standard open orchidopexy

Study (year) Period of operations	Study methods	Definition of success	Patient age	Patient characteristics	No. testes	Success rate	Complications	Atrophy	Reoperation
Lintula[65] (2008) Operations: 1992-2004	Retrospective Mean f-up: 30 mos	Mid-low scrotal position and no atropy Equal in size vs. contralateral testis	2.5 yrs (1-10)	Intraabdominal testes Unilateral	18 (18 children)	9(53%) normal size Position 14(82%) low- mid scrotal 3(18%) high or inguinal	1 (6%) scrotal hematoma 1 (6%) readmission outpatient clinic	1 (6%)	3 (18%) atrophy or unacceptable position (no additional information)

f-up = follow-up ; mos = months ; yr = year
* Based on full cohort, 447 testis

Table 16 Study results, non-palpable testes, direct laparoscopic orchidopexy

Study (year) Period of operations	Methods	Definition of success	# testes	Mean age	Patient characteristics	Success rate	Atrophy	Complications	Reoperations / changes in surgery
Lintula[65] (2008) Operations: 1992-2004	Retrospective Mean f-up: 30 mos	Mid-low scrotal position and no atropy Normal: equal in size vs. contralateral testis	19 (16 patients)	2.5 yrs (1-13)	Intraabdominal	10 (53%) normal size **Position** 16 (88%) low – mid scrotal 2 (12%) high-vanished	1 (6%)	Wound infection 1 (6%) Readmission outpatient clinic 2 (11%)	**Reoperations** 2 (11%) atrophy or unacceptable position **Changes** 1/16 (6%) change to open surgery§ 1/16 (6%) 1-step FS
Palmer[66] (2008) Operations: 2001-2007	Retrospective f-up: ≥ 4m	Lack of atrophy or malposition	64 patients	10 mos (8-48)	Intraabdominal , contralateral processus vaginalis	**Short and long-term** 64 (100%)	0	Zero hematoma or infection	0
Kaye[67] (2008) Operations: 2000-2006	Retrospective F-up: 1yr	Normal size and position	42 (26 patients)	9 mos (7-52)	Bilateral intraabdominal	Mid-lower scrotum 38/42 (90.4%)		6-12 mos 2 (4.8%)	1 (2.4%)¶ Change to FS*: 4/42 (9.5%)
Yucel[68] (2007) Operations 2000-2006	Retrospective f-up: 1-25 mos	Testicular viability, no atrophy	46 (44 patients)	Low scrotum 12 mos (6-24) High 35 mos (7-183)	Intraabdominal (within 2 cm of internal ring)	**Low scrotum** 20/20 (100%) 18(90%) at f-up **High scrotum** Laparoscopy 0 (all in high scrotum) 1-step FS (lapar) 10/12 (83%) at f-up: 7 (70%)	Low 2 (10%) High 4/22 (18%)	NR	Reoperations according to Initial position Low scrotum: 0 High scrotum: 5/22 (22.7%)
Yucel[68]	Retrospective	Testicular	6-12 mos: 21		Intraabdominal	12/21 (57%)	NR	NR	NR

(2007) Operations 2000-2006 Age stratified	f-up: 1-25 mos	viability, no atrophy	6-24 mos: 38	(within 2 cm of internal ring)	20/38 (52.6%)			

cm = centimeter ; FS = Fowler-Stephens procedure ;f-up = follow-up ; lapar = laparoscopy ; mos = months ; US = ultrasonography ; yr = year
§ Child had previous operation on high perforated anus.
¶ One patient underwent secondary open surgery three months later to relocate the testis that had been brought down by 1 stage Fowler-Stephens procedure.
*Due to insufficient cord length without vessel ligation and transaction the operation technique was changed to 1 or 2-stage Fowler-Stephens procedure.

Table 17 Study results, non-palpable testes, Fowler-Stephens orchidopexy

Study (year) Operations	Methods	Definition of success	Number of testes	Technique	Mean age surgery	Patient characteristics	Success rate	Atrophy	Complications	Reoperations
2-stage Fowler-Stephens orchidopexy										
Robertson[69] (2007) Operations: 1996-2004	Retrospective f-up: 18 mos	Testis size and position	25 (21 patients)	1st stage lapar. (all) 2nd stage lapar. 21 (84%) 6 mos btw stages	36 mos (11-68)	Unilateral: 17 (81%) intraabdominal	**Scrotal position** 22 (88%) F-up:16/18* (89%) **Good-reasonable size** 17 (68%) F-up: 12/18 (67%)	3 (12%)	Wound infection: 1 (4%)	NR
1-stage Fowler Stephens orchidopexy										
Horasanli[70] (2006) Operations over 9 years	Prospective F-up: 12 mos	Good scrotal position, size, and adequate blood flow (Doppler)	24 (22 patients)	Open surgery	2 yrs (1.5-4)	Unilateral: 20(91%) Internal inguinal ring or adjacent	1st week 24 (100%) 3-12 mos 21 (87.5%)	3 (12.5%) hypoplasia and inadequate blood flow	NR	NR

Btw = between ; f-up = follow-up ; mos = months ; NR = not reported ; yr = year
* Seven testes not evaluated as patients were lost to follow-up.

Table 18 Study results, palpable testes, scrotal orchidopexy

Study (year) Period of operations	Methods	Definition of success	Number of testes	Mean age	Patient characteristics	Success rate	Atrophy	Complications	Reoperations
Low transscrotal orchidopexy									
Takahashi[71] (2009) Operations: 1996-2005	Retrospective Median follow-up: 39.1 mos	Position	49 (32 patients)	Median: 3.3 years (1-10)	Processus vaginalis 14(28.6%) patent 34 (69.4%) obliterated	48 (97.7%) good position in scrotum and good consistency	0	None* 0	1 (2.3%) testis ascended postoperatively requiring inguinal orchidopexy
Scrotal orchidopexy									
Dayanc[72] (2007) Operations: 2001-2005	Prospective Mean f-up: 29.4 mos	Testicular position and size complications	204	2.2 years (10 mos-12 yrs)	Location 128 (63%) distal to the external inguinal ring 76 (37%) inguinal	All: 192(94.1%) Distal: 124 (96.9%) Inguinal: 68 (89.5%)	0 (on f-up)	0 (on f-up)	Change inguinal orchidopexy required§ 12/204 (5.9%)

f-up follow-up ; mos months ; NR not reported ; yr year
* Other complications absent: Inguinal hernias, hydroceles, wound infection, hematoma.
§ Change to traditional inguinal orchidopexy because of being together with the inguinal hernia and inadequate mobilitzation.

Table 19 Study results, palpable testes, other orchidopexy

Study	Study methods	Definition of success	# testes	Mean age	Patient characteristics	Success rate	Atrophy	Complications	Re-operation
Laparoscopic orchidopexy									
He[73] (2008) Operations: 2005-2006	Prospective f-up: 6-12m	Testis position	103	17 mos (8-72)	Inguinal canal (all) Unilateral: 77 (86%)	103(100%) successful scrotal sac corrections F-up: good size and correct position	0	1 (1.1%) epigastric vessel bleeding (1st operation)	0
Ballon inflation-created subdartos pouch orchidopexy (palpable and non-palpable									
Al-Saied[74] (2008) Operations: 2007-2008	Prospective Mean f-up: 12m	Testis position and lack of atrophy	75 patients	13 mos (3-36)	53 (71%) palpable 22 (29%) non-palpable	Palpable testis 53 (100%) Non-palpable 20 (91%) presumed given 2 cases with small size testes	0 (palpable) 0 (non-palpable)*	0 (hematoma or infection)	NR

f-up follow-up ; mos months ; NR not reported
*Assumed no atrophy judged by the fact that although two testicles had small size, atrophy was not mentioned by the authors

2.2.2 Study results, hormone treatment of cryptorchidism

Two meta-analyses and one systematic review on hormone treatment alone for cryptorchidism were identified. The meta-analyses included similar studies with 3-4 studies not in common. The systematic review included three RCTs not included in the meta-analyses. These three studies do not include a placebo alone comparison which was the control group in the meta-analyses.

Table 20 Study results, meta-analyses on hormone treatment of cryptorchidism

Study	RCTs included	Methods Meta-analysis	Hormone treatment / Duration	N. patients (hormone/control)	Patient charact	Definition of response	Success rate (95% CI)	Measure of Association (95% CI)	Relapse rate	Comments
Henna[23] (2004) F-up:NR	2 RCTs	Fixed-effects Peto	hCG IM (A) vs. (B) GnRH intranasal Duration not provided	201 (102 / 99) Bilateral 109 (51 / 58) Unilateral 92 (51 / 41)	May include retractable testes	Complete testicular descent	A: 25% B: 18%	ARR 7% (1.2 , 17)	NR	Moderate risk of bias, not proper allocation concealment
Henna[23] (2004) F-up:NR	9 RCTs	Fixed-effects Peto	GnRH intranasal (A) vs. placebo (B) Duration not provided	1,049 (585 / 544)	May include retractable testes	Complete testicular descent	A: 19% B: 5%	OR 3.59 (2.52 , 5.12) AR: 14%¶	NR	
Pyorala[24] (1995) F-up:NR	9 RCTs	Mantel Haenszel	LHRH (A) vs. placebo (B) HCG vs. placebo Duration 1 day-4wks (LHRH)§ 1wk-12m (hCG)	872	Includes retractable testes	Complete testicular descent at the end of treatment	11 RCTs A: 21% (18 , 24) B: 4% (2-6%) HCG: 19%	9 RCTs RR 3.21 (1.83 , 5.64) ARR 10%¶	NR	
Pyorala[24] (1995) F-up:NR	4 RCTs non-retractile testes	Mantel Haenszel	LHRH (A) vs. placebo (B)	NR	Non-retractile testes	As above	A:12% (8 ,15) B: 5% (2 , 7) HCG: 19%	4 RCTs RR 2.57 (1.39 , 4.74) ARR: 7%¶	5 RCTs 24% (13,35) f-up ?	
Pyorala[24] (1995) F-up:NR	Testes position RCTs and non-	Mantel Haenszel	(A) LHRH or HCG vs. (B) placebo	NR	Includes retractable testes	As above	Intraabdominal 14% (12 , 17) Inguinal 47%	N/A	NR	

	RCTs						(44 , 49) Prescrotal 59% (53 , 64) High scrotal 57% (45 , 69)			
Pyorala[2] [4] (1995) F-up:NR	Age < 4yrs vs. >4 yrs 4 RCTs	Mantel Haenszel	(A) LHRH or HCG vs. (B) placebo	NR	Includes retractable testes	As above	Data from a graph < 4yrs A:25% vs. B: 5% > 4 yrs A:15% vs. B:3%	Overlapping CIs btw hormone groups (no significant difference) Values not reported	NR	

ARR = absolute risk reduction ; CI = confidence interval ; HCG = human chorionic gonadotropin ; IM = intramuscular ; LHRH = luteinizing hormone releasing hormone ; N/A = not applicable ; OR = odds ratio ; RCT = randomized controlled trial ; RR = relative risk

*Christiansen 1988 not included – reason ? 1992 may be an update

§ Trials with different treatment duration pooled together since treatment response was not associated with treatment length

¶ AR (absolute risk) calculated based on the crude rates.

Table 21 Study results, systematic review by Ong et al. RCTs not included in meta-analyses

Study	Hormone treatment	N. patients (hormone/control)	Patient characteristics	Definition of response	Success rate (hormone)	Success rate (placebo)	Relapse rate	Variance Statistical test
Hoorweg-Nijman From Ong et al.[25]	FSH+HCG (A) vs. placebo (B) +HCG	22 (14 / 8)	NR	NR	5 (33%)	Placebo+ HCG 5 (60%)	NR	NR
Bertelloni From Ong et al.[25]	HCG vs. HCG+HMG vs. GnRH vs. GnRH+HCG	155 (37 / 39 / 39 / 40)	NR	NR	7 (19%) HCG 5 (13%) HCG+HMG 5(13%) GnRH 6(15%) GnRH+HCG	N/A	36 (23%)	NR
Esposito From Ong et al.[25]	HCG vs. HMG vs. LHRH vs. HMG+HCG vs. LHRH	324 (113 / 35 / 85 / 27 / 64)	NR	NR	40 (35%) HCG 0 HMG 25 (25%) HMG+HCG 19 (30%) LHRH+HCG	N/A	NR	NR

ARR absolute risk reduction ; FSH folicule-stimulating hormone ; GnRH gonadotropin-releasing hormone ; HCG human chorionic gonadotropin ; HMG human menopausal gonadotropin ; LHRH luteinizing hormone releasing hormone ; N/A not applicable ; NR not reported ; OR odds ratio ; RCT randomized controlled trial ; RR relative risk

2.2.3 Study results, observational non-comparative studies of orchidopexy effects on fertility

Systematic reviews and meta-analyses were part of the inclusion criteria, however none was identified.

The results of the studies identified are summarized below. Only outcomes in children < 4 years were summarized.

Table 22 Study results, observational studies, effect on fertility (cell count)

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Sperm count
Hadziselimovic[39] (2007) Unilateral UDT results provided	Prospective Evaluations at 21-25 yrs Age breakdown (post-hoc§) < 3yrs vs. > 8 yrs at surgery	Orchidopexy Failed hormone treatment before surgery Unilateral or bilateral	Infertility* Sperm count Ad spermatogonia	218 (255 testes) Unilateral < 3yrs: 28 > 8yrs: 96 231 patients in original list	10 mos-11 yrs	Palpable: 238 (93.3%) Unilateral: 181 (83%) HCG before surgery: 100%	**Unilateral only¦** At 21-25 yrs age <3 yrs§ 120x10^6/ejac¶ > 8 yrs 40 x10^6/ejac¶ p=.0012
Coughlin[27] (1999) 1955-1974 Unilateral Patients in male fertility study	Prospective measurements in adulthood	Men who underwent orchidopexy **Patients in male fertility study (not clear if patients have fertility problems)**	Inhibin B FSH LH Testosterone Sperm density	84 patients 0-2yrs: 10 2-5yrs: 20 >5yrs: 54	6.3 yrs (1 mos-11 yrs)	Unilateral (100%)	**Sperm density In adulthood§§** X 10^6/ml 0-2yrs: 59.8±42 2-5yrs:48±47 5-8yrs:46±34 8-11yrs:53±52 p=.846

HCG = human chorionic gonadotropin ; mos = months ; spermat = spermatogonia ; UDT = undescended testis ; yr = year
* Infertility: sperm concentration < 40 x 10^6 per ejaculate (after 5 days of abstinence). 2nd ejaculate analyzed in case the 1st had sperm count below the fertility limit, highest value used.
§ Age breakdown for subgroups not pre-defined in methods but decided post-hoc based on results.
¶ Values derived from a graph, exact figures not provided. Median values seem to have been provided.
¦ Bilateral undescendent testis, n=37, stratified analyses not performed
§§ Age at measurement not specified

Table 22 cont. Observational studies, effect on fertility (cell count)

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Sperm count (in adulthood)
Engeler[28] (2000) 1970-1979 Bilateral UDT	Prospective measurements in adulthood	Bilateral UDT (for fertility evaluation) Not retractile	Sperm concentration Motility Normal forms	35 available 0-2yrs:14 >2yrs:21 only 24 (12 each) agreed to semen analysis	At surgery 0-2yrs (A): 1.5 yrs (0.9-1.9) >2yrs (B): 6.8 yrs (2.1-13.8) At measurement A:22 yrs(19-30) B:32 yrs(21-40)	Bilateral (100%)	**Normal** 0-2yrs: 8 (67%) >2yrs: 3 (25%) **Oligospermia¶¶** 0-2yrs: 2 (17%) >2yrs:8 (67%) **Azoospermia** 0-2yrs: 2(25%) >2yrs: 1(12.5%)
Chilvers[29] (1995) Bilateral UDT	Systematic review Age breakdown: <9 yrs or > 9 yrs (not included due to high age breakdown)	Studies that evaluated adult fertility with regards to treatment of UDT Excludes men selected at fertility clinics or for treatment of vasectomy	Sperm concentration (azoospermia, oligospermia)	248 (bilateral)	NR	Bilateral (100%)	**Oligospermia¶¶** Orchidopexy alone 49/156 (31%) Orchidopexy±hormones 76/248 (31%) **Azoospermia** Orchidopexy alone 65/156 (42%) Orchidopexy±hormones 105/248 (42%)
Chilvers[29] (1995) Unilateral UDT	Systematic review Age breakdown: <9 yrs or > 9 yrs (not included due to high age	Studies that evaluated adult fertility with regards to treatment of UDT Excludes men selected at fertility	Sperm concentration (azoospermia, oligospermia)	519 (unilateral)	NR	Unilateral(100 %)	**Oligospermia¶¶** Orchidopexy alone 98/308 (32%) Orchidopexy±hormones 124/406 (31%) **Azoospermia**

	breakdown)	clinics or for treatment of vasectomy					Orchidopexy alone 66/379 (17%) Orchidopexy±hormones 72/519 (14%)

HCG = human chorionic gonadotropin ; mos = months ; spermat = spermatogonia ; UDT = undescended testis ; yr = year
¶¶ Oligospermia: < 20 million sperm per milliliter

Table 23 Study results, observational studies, effect on fertility (normal sperm count and motility)

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Sperm motility	Normal sperm forms
Engeler[28] (2000) 1970-1979 Bilateral UDT	Prospective measurements in adulthood	Bilateral UDT (for fertility evaluation)	Sperm concentration	35 available 0-2yrs:14 >2yrs:21 only 24 (12 each) agreed to semen analysis	At surgery 0-2yrs (A): 1.5 yrs (0.9-1.9) >2yrs (B): 6.8 yrs (2.1-13.8) At measurement A:22 yrs (19-30) B:32 yrs (21-40)	Bilateral (100%)	Motile 0-2yrs: 50% (4-66) >2yrs: 40% (22-75) Progressive 0-2yrs: 42% (4-60) >2yrs: 25% (17-65) (n=9)	Normal 0-2yrs: 34% (9-60) >2yrs: 24% (8-41)

CI = confidence interval ; f-up = follow-up ; HCG = human gonadotropin hormone ; mos = months ; SD = standard deviation ; UDT = undescended testis ; yr = year

Table 24 Study results, observational studies, effect on fertility (testicular size and volume)

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Testicular size	Testicular volume
Engeler[28] (2000) 1970-1979 Bilateral UDT	Prospective measurements in adulthood	Bilateral UDT (for fertility evaluation)	Sperm concentration	35 available 0-2yrs:14 >2yrs:21 24 (12 each) agreed to semen analysis	At surgery 0-2yrs (A): 1.5 yrs (0.9-1.9) >2yrs (B): 6.8 yrs (2.1-13.8) At measurement A:22 yrs (19-30) B:32 yrs (21-40)	Bilateral (100%)	NR	**In adulthood** Right testes 0-2yrs: 21ml(10-36) p=.005 >2yrs: 13ml (6-33) Left testes 0-2yrs: 14ml(10-21) p=.19 >2yrs: 11ml (7-26)
Taskinen[30] (1997) 1966-1977 Unialteral/bilateral	Prospective measurements in adulthood	Healthy patients Orchidopexy < 4 yrs Unilateral or bilateral UDT	Testicular volume	73/149 responded when contacted	10 mos-7 yrs at surgery 0-2yrs: 22 testes (25%) 3-5 yrs:44(50%) 6-13 yrs: 22 (25%) At measurement 16-30 yrs (at measurement)	Unilateral: 58 (79%) HCG bef. surgery: 26 (36%) Descended testes at measurement: 100%	Difference in size between cryptorchid and normally descended testis statistically significant (p<.001) not stratified by age Consistent slight decrease in testis size with higher locations before surgery	**In adulthood** Volume of each UDT by age at surgery (mean±SD) 0-2yrs: 11±5ml 3-5yrs: 13±7ml 6-13yrs:9±5ml Surgery after 5 yrs of age: testes were smaller in adulthood, but not statistically significant.

Bef.= before ; CI = confidence interval ; f-up = follow-up ; HCG = human gonadotropin hormone ; mos = months ; SD = standard deviation ; UDT = undescended testis ; yr = year

Table 25 Study results, observational studies, effect on fertility (hormones)

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Inhibin B	FSH	Testosterone
Coughlin[27] (1999) 1955-1974 Unilateral Patients in male fertility study	Retrospective Subjects contacted by questionnaire	Men who underwent orchidopexy **Patients in male fertility study (not clear if patients had fertility problems)**	Inhibin B FSH LH Testosterone Sperm density	84 0-2yrs: 10 2-5yrs: 20 >5yrs: 54	6.3 yrs (1 mos-11 yrs)	Unilateral (100%) Not clear if patients are infertile2	**In adulthood*** Normal:73-330 pg/ml 0-2yrs: 158±59 2-5yrs: 106±54 5-8yrs:121±59 8-11yrs:104±36 p=.032 linear trend	**In adulthood*** Normal:1.1-7.9 units/L 0-2yrs:4.4±3 2-5yrs:6.1±3 5-8yrs:6.5±6 8-11yrs:7.4±4 p=.088	**In adulthood*** Normal:285-980 ng/dl 0-2yrs:653±118 2-5yrs:656±171 5-8yrs:570±143 8-11yrs:557±193 p=.029 linear trend
Lee[31] (2002) 1955-1974 Unilateral	Men with orchidopexy compared to age-matched controls¦¦	Men with orchidopexy Unilateral cryptorchidism	Testosterone levels according to age at surgery	106 (A, cryptorchid) 52 (B, controls)	A: 7.3 ±4 yrs B:6.7±3 yrs	Unilateral (100%)	NR	NR	Negative correlation of adult testosterone values with age at orchidopexy Corr: -0.272,p=.005 Values not provided

CI = confidence interval ; corr = correlation ; FSH = follicle stimulating hormone ; f-up = follow-up ; LH = luteinizing hormone ; mos = months ; NR = not reported ; UDT = undescended testis ; yr = year
*Age at measurement not specified
¦¦ Men who underwent surgery for unrelated condition during the same period.

Table 26 Study results, observational studies, effect on fertility (paternity)

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Paternity / Fertility
Lee[32] (2001) Unilateral	Retrospective Stratified by age group (0-2yrs, 3-5yrs, 6-8yrs, 9-11yrs, >11yrs)	Men with information on testis size and paternity	Testis size at surgery Paternity* Unsuccessful attempt* Broken down by age groups	166	Approx. 8yrs	Unilateral (100%) Surgery outcomes Small testis: 89 (91%) Atrophic: 18 (94.7%) Normal: 57 (87.7%)	Full cohort (in adulthood) Paternity: 164 (90.1%) No difference based on testicular size at surgery No difference according to age of surgery (0-2yrs, 3-5yrs, 6-8yrs, 9-11yrs, >11yrs) Values not provided
Hadziselimovic[39] (2006) Unilateral/bilateral	Prospective Evaluations at 21-25 yrs Age breakdown < 3yrs vs. > 8 yrs§	Orchidopexy Failed hormone treatment before surgery Unilateral or bilateral	Infertility¶ Sperm count Ad spermatogonia	218 (255 testes) Unilateral < 3yrs: 28 > 8yrs: 96	10 mos-11 yrs	Palpable: 238 (93.3%) Unilateral: 181 (83%)	**Unilateral only¦** **% Infertile* in patients with Ad spermat. after surgery**** <3yrs (n=28): 3.6% (95% CI: 0.1,18) >4 yrs (n=46): 9.5% (95% CI: 3 , 23)

CI = confidence interval ; FSH = follicle-stimulating hormone ; Info = information ; LH= luteinizing hormone ; UDT = undescended testis
*Definitions: Paternity: men who fathered at least one child.
Unsuccessful attempt: no paternity after more than 12 months of attempts.
** In patients without Ad spermatogonia after surgery, no statistically difference was found in the % patients considered infertile* at 21-25 years of age by age at surgery: ≤ 3 years of age: 75% (95% CI: 43 , 95), ≥ 4 years of age: 70.5% (95% CI: 60 , 79)
¦ Bilateral undescendent testis, n=37, stratified analyses not performed
¶ sperm concentration < 40 x 10^6 per ejaculate (after 5 days of abstinence). 2nd ejaculate analyzed in case the 1st had sperm count below the fertility limit, highest value used
§ Age subgroups defined post-hoc based on study results.

Table 26 cont. Study results, observational studies, effect on fertility (paternity)

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Paternity / Fertility
Lee[33] (1995) Operations: 1955-1969 Unilateral/bilateral	Prospective evaluation in adulthood (questionnaire survey) Orchidopexy data retrospectively collected Control group non-cryptorchid men	Orchidopexy Control: non-cryptorchid men who underwent tonsillectomy. Age- and surgery date-matched	Paternity	363 patients Control: 336 patients	1 mos-15 yrs	Unilateral: 313(86%)	**Values by age group not provided** **Paternity by age group** No statistically significant difference in paternity rate or length of time of attempt to conception according to age at orchidopexy (includes < 1 yr to 15 yrs broken down by age). **Paternity (full cohort, <1-15yrs)** No statistically significant difference in paternity was found btw previous unilateral UDT (75%) and control (73%)§. Difference statistically significant for bilateral UDT (56%) vs. control (76%) p<.005 §
Miller[34] (2001) Operations: 1955-1975 Unilateral	Retrospective for surgery data. Prospective: questionnaire survey in adulthood	Unilateral UDT Orchidopexy Men who fathered a child or attempted > 12 mos Control: unrelated surgery in same period at the hospital matched for age at surgery	Paternity	359 (control: 443)	0 - >11 yrs	Unilateral (100%)	**Paternity by age (among those who attempted > 12 mos)** Age at surgery (orchidopexy‼) 0-1.9 yrs: 20/23 (87%) 2-4.9yrs: 43/47 (91.5%) 5-7.9yrs: 61/71 (85.9%) 8-10.9yrs: 72/84 (85.7%) >10.9yrs: 71/79 (89.9%) Total (not broken down by age): Orchidopexy: 322/359 (89.7%) Control: 413/443 (93.2%)

Cendron[35] (1989) Operations: 1950-1960	Retrospective for surgery data. Patients contacted by phone	Orchiopexy with testicular biopsy	Paternity	37* 0-4yrs: 8	7 yrs (1-14)	Unilateral: 30 (75%) Unilateral (0-4yrs): 5(63%)	Paternity according to age at surgery 0-4 yrs: 5/8 (63%) (unilateral:4/5, 80%, bilateral: 1/3. 33%) ≥ 5 yrs: 19/25 (76%) (unilateral: 17/19, 89%, bilateral: 2/6, 33%)

Btw = between CI = confidence interval ; FSH = follicle-stimulating hormone ; Info = information ; LH = luteinizing hormone ; UDT = undescended testis
§ Values for currently or previously married men.
¦¦ Paternity rate in controls not stratified by age.
* 40 patients were contacted by phone, 37 agreed to participate

2.2.4 Study results, impact of orchidopexy and cryptorchidism on malignancy

Includes meta-analyses and systematic reviews on the effect of orchidopexy on testicular cancer were identified. Individual studies published after the period covered in the search strategies of systematic reviews and meta-analyses were identified.

Table 27 Characteristics, systematic reviews and meta-analyses, malignancy

Study	Type of study	SR search methods	Patient characteristics	# studies	Outcome measured
Wood[45] (2009)	Systematic review	Publications from 1950 on (latest 2007) Case series, cohort or case-control studies, and meta-analyses	Cryptorchidism who underwent orchidopexy	6 retrospective cohort 2 meta-analyses 3 case-control 3 non-comparative, others	Risk ratio of malignancy vs. population without cryptorchidism
Walsh[43] (2007)	Meta-analysis	Publications from 1996-2006	Cryptorchidism who underwent orchidopexy	2 cohort 3 case-control	Odds ratio or risk ratio of malignancy if orchidopexy is performed after age 10-11 yrs vs. before that
Tuazon[44] (2008)	Meta-analysis	Updated Walsh et al. (included 2 additional publications from 1985 and 1994)	Cryptorchidism who underwent orchidopexy	Studies included in Walsh et al. plus 2 studies and 1 more recent data from a cohort study	Odds ratio or risk ratio of malignancy if orchidopexy is performed after age 10-11 yrs vs. before that

Table 28 Characteristics, observational studies, malignancy

Study	Type of study	Country	Patient identification	Source of data	Analyses Variables adjusted for	Outcome measured	F-up
Pettersson[46] (2007)	Cohort	Sweden	Cryptorchidism (ICD codes) and < 20 yrs old at orchidopexy National database Period: 1965-2000	National databases	F-up period Region where surgery was done	Testicular cancer (seminomas, nonseminomas) identified through linkage to National Cancer Registry Results stratified by age	F-up from 15yrs age or 1 yr after surgery until Dec. 31st 2000, age 55, outcome, emigration or death
Myrup[48] (2007) (replicated Pettersson[46] methods in Danish cohort	Cohort	Danemark	According to Petterson et al. Period: 1977-2003	National databases	NR	Testicular cancer (methods as above)	As above but f-up until Dec. 31st 2003
Dusek[47] (2008)	Case-control	Czech Republic	Cases: TGCC cases identified (ICD-10) from 2 hospitals Period 2000-2006 Controls: age-matched healthy men identified in the same hospitals¦ Period 2005-2007	Patient questionnaire and hospital pathology report	Unconditional logistic regression¶ Variables include: patient and maternal history, lifestyle Analyses stratified by cancer type	TGCC stratified by seminoma and non-seminoma	Retrospective study

F-up = follow-up ; ICD = International Statistical Classification of Diseases and Related Health Problems ; NR = not reported ; SR = systematic review ; TGCC = testicular germ cell cancer

¦ Controls identified through blood donors, men accompanying patients, and hospital personnel

¶ Univariate and multivariate analyses. Only variables that were statistically significant were maintained in the multivariate analyses.

Table 29 Results, systematic reviews and meta-analyses (effects on malignancy)

Study (year)	Type of study	Studies included	No. patients	RR of testicular cancer (95% CI)	Comments
Wood[45] (2009)	Systematic review of observational studies	5 case-controls 5 database studies	240 -16,983 depending on study	Cryptorchidism vs. no cryptorchidism RR 2.75 – 8 OR 3.82 (1 study) No confidence interval reported	Some studies included evaluated the effects of age at orchidopexy
Walsh[43] (2007)	Meta-analysis of observational studies	2 case-cohorts 3 case-control	28 - 2,914 depending on study	Orchidopexy after 10-11 yrs vs. before OR 3.4 (0.7 , 17.7)	Authors comments: Prepubertal orchidopexy (<10-11 yrs) may decrease the risk of testicular cancer.
Tuazon[44] (2008)	Meta-analysis of observational studies	Studies in Walsh et al. [43] plus 2 studies and updated data on 1 study	Not provided	Orchidopexy after 10-11 yrs vs. before OR 2.7 (1.1 , 6.3)	Authors comments: Some confounders could not be accounted for such as patients with a different risks of testicular cancer such as spontaneous testis descent. These limitations hinder the interpretation of the effect of orchidopexy

CI = confidence interval ; NR = not reported ; OR = odds ratio ; RR = relative risk

Table 30 Results of observational studies (effects on malignancy)

Study (year)	Type of study	Inclusion criteria	Outcome	No. patients Person-yrs	# Cases	RR (95% CI) of testicular cancer	Author's conclusions
Myrup[48] (2007) Danemark	Cohort	Replicated Pettersson et al. [46] methods on Danish cohort	As per Petterson et al. [46]	21,488 patients 192,067 person-yrs	110 (all) 0-6yrs: 5 0-12yrs:55 13-19yrs: 55	vs. general population All: 3.73 (3.09 , 4.5) 0-6 yrs: 3.66 (1.53 , 8.8) 0-12 yrs: 3.78 (2.9 , 4.93) 13-19yrs: 3.68 (2.83 , 4.8) Results on additional subgroups provided	The authors found that risk of cancer did not vary by age of orchidopexy. Risk may be determined in utero
Pettersson [46] (2007) Sweden	Cohort	Cryptorchidism (ICD-9) Men who underwent orchidopexy <20 yrs	TGCC (seminomas and non-seminomas*) Censoring: age 55 yrs, death, emigration, Dec. 31st 2000	16,983 patients 209,984 person-yrs Mean f-up: 12.4 yrs	56 (all) 0-6yrs: 9 < 13yrs: 38 ≥13 yrs: 18	Standardized incidence ratio (95% CI)¶ vs. general population All: 2.75 (2.08 , 3.57) 0-6yrs: 2.02 (0.93 , 3.84) <13 yrs: 2.23 (1.58, 3.06) ≥13 yrs: 5.4 (3.2 , 8.53) Additional categories provided	Risk of testicular cancer in ≥13yr-olds almost 2x that of <13yr-olds Unknown confounders associated with calendar time may be present Inclusion of acquired and congenital UDT may affect outcome[75]§

CI = confidence interval ; RR = risk ratio ; TGCC = testicular germ cell carcinoma ; yrs = years
*Included teratomas, choriocarcinomas, yolk-sac tumours, embryonal carcinomas, and mixed germ-cell tumours
¶ Covariates: calendar period of follow-up and of surgery, region where orchidopexy was performed
§ Same may be said for Myrup et al. since the same inclusion criteria as Petterson et al. were used

Table 30 cont. Observational studies, results

Study (year)	Type of study	Inclusion criteria	Outcome	# Cases	OR (95% CI) of testicular cancer	Author's conclusions
Dusek[47] (2008) Czech Republic	Case-control	Cases: TGCC cases identified (ICD-10) from 2 hospitals Controls: age-matched healthy men identified in the same hospitals	TGCC (seminoma and non-seminoma)	Cases: 356 (195 seminoma, 161, non-seminoma) Controls: 317	TGCC¦ (356 cases) Univariate analyses Orchidopexy < 5 yrs age: 5.24 (1.5, 18.1) Multivariate analysis* History of cryptorchidism: 3.86 (2.46 , 5.7) Atrophy: 5.88 (2, 16.8) Prostate ca, family: 4.8(2.3,16.8) Low education and manual occ.: 3.01 (2.15 , 5.41) Breast ca, family: 2.01(1.1,3.7) Birth weight<3kg: 1.67(1 , 2.6)	Several factors are implicated in TGCC without being able to single out stronger predictors among them.

ca = cancer ; CI = confidence interval ; occ = occupation; OR = odds ratio ; TGCC = testicular germ cell carcinoma ; yrs = years
¦ Separate analysis dividing TGCC cases into seminoma and non-seminoma are provided in the publication
* Orchidopexy not included in the multivariate analysis. Only variables that were statistically significant were maintained in the multivariate analyses.

2.2.5 Study results, testicular histology according to age

Table 31 Study results, testicular histology

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Cell count
Hadziselimovic[39] (2007) Unilateral	Prospective Evaluations at 21-25 yrs Age breakdown (post-hoc§) < 3yrs vs. > 8 yrs at surgery	Orchidopexy Failed hormone treatment before surgery Unilateral UDT	Sperm count	218 (255 testes) Unilateral < 3yrs: 28 > 8yrs: 96 231 patients in original list	10 mos-11 yrs	Palpable: 238 (93.3%) Unilateral: 181 (83%) HCG before surgery: 100%	**Sperm count** **Unilateral only** At 21-25 yrs age <3 yrs§ 120x10^6/ejac¶ > 8 yrs 40 x10^6/ejac¶ p=.0012
Hadziselimovic[37] (2001) Unilateral/bilateral	Prospective Comparative: surgery at < 6 mos vs. > 6 mos	Orchidopexy with testicular biopsy before 2 yrs age	Germ cell count/tubulus	31 patients < 6 mos at surgery: 14 > 6 mos at surgery: 17	Surgery < 2 yrs age	Unilateral: 25 (81%)	**Mean germ cell/tubulus*** < 6 mos: 5/tubulus > 6 mos: 0.5/tubulus p<.0001
Hadziselimovic[38] (2001)	Prospective Compares counts at different age at surgery	Orchidopexy with testicular biopsy before 2 yrs age	Germ cells/tbcx	27 patients At surgery: < 6 mos:14 6-24 mos: 13	Before < 2 yrs	Unilateral: 21 (78%)	**Mean germ cells/tbcx** < 6 mos: 5.2 6-24 mos: 0.48

¶ Approximate values (from graph)

Table 32 Study results, testicular histology

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Cell count
Hadziselimovic[36] (2004)	Prospective Compares counts at different age vs. contralateral and control group (not explained how it was identified)	Testicular biopsies Unilateral UDT Unclear if underwent surgery	Ad spermagogoina / tbcx	# biopsies 125 UDT 111 contralateral testis 50 controls	No surgery ?	Unilateral:100 %	**Mean Ad spermatogonia/tbcx** **1-5 mos** UDT: 0.01 Contral.:0.03 Control:0.03 p<.05 **6-8 mos** UDT: 0 Contral.:0.08 Control:0.2 p<.01 **During 1st 12 mos** UDT: 0.01 Contral.:0.08 Control:0.1 p<.01

Table 33 Study results, testicular histology

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Cell count
Huff[40] (1993) Unilateral	Prospective Compares UDT vs. contralateral (CDT) testis in age groups	Orchidopexy with testicular biopsy	Total germ cells / tubule	# biopsies UDT: 399 CDT: 356	Stratified by age group	Unilateral: 100%	**Mean total germ cells / tubule ±SD** **0-5 mos** p=.715 UDT:2.3±1.94 CDT: 3.3±2.45 **6-11 mos** p=.4504 UDT: 1.98±1.92 CDT: 1.93±1.4 **12-17mos** p<.0001 UDT: 0.84±0.84 CDT: 1.42±1.11 **18-23 mos** p<.0001 UDT: 0.35 ±0.42 CDT: 1.54±1.16 **3-4yrs** p<.0001 UDT: 0.31±0.53 CDT: 2.15±2.16 **5-9yrs** p<.0001 UDT: 0.54±0.7 CDT:2.77±2.66 p<.0001 between UDT and CDT in age groups 12 mos and older

Table 34 Study results, testicular histology

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N. patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Cell count
Huff[40] (1993) Unilateral	Prospective Compares UDT vs. contralateral (CDT) testis in age groups	Orchidopexy with testicular biopsy	Biopsies with adult Ad spermatogonia	# biopsies UDT: 399 CDT: 356	Stratified by age group	Unilateral: 100%	**% biopsies with adult Ad spermatogonia** **0-5 mos p=1** UDT:4 (80%) CDT: 5 (100%) **6-11 mos p=.0225** UDT: 35 (65%) CDT: 44 (82%) **12-17mos p<.0001** UDT: 46 (55%) CDT: 69 (83%) **18-23 mos p=.0072** UDT: 25 (53%) CDT: 38 (81%) **3-4yrs p<.0001** UDT: 20 (25%) CDT: 63 (80%) **5-9yrs p<.0001** UDT: 27 (28%) CDT:77 (79%)

Table 35 Study results, testicular histology

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Cell count
Park[16] (2007) **Operations:** **1998-2001** **1996-2005** **(controls)**	Retrospective Comparing different age groups	NR	Hystological parameters*, mean tubular diameter (MTD), sertoli cell index	65 testes	Stratified by age group	Unilateral (100%) Inguinal position (100%)	**Histological parameters¦:** ≤ 1yr: higher vs. >1yr (p<.001) Testicular volume, MTD, SCI – not statistically significantly different among age groups
Huff[41] (1989)	Prospective	Unilateral UDT Orchidopexy with biopsy Excluded: retractile, absent, ectopic		232 (UDT) 195 (CDT)	1 mo-13 yrs	Unilateral (100%)	**Mean germ cells (data in graph)** Curves of UDT and normal testis statistically not different until 2 yrs. Thereafter UDT drops to far below normal and stays that way (up to 14yrs) – Authors words (p<.0004) **Maturation of germ cells** (gonocytes begin to disappear in normals shortly after birth and are absent in almost all biopsies after 6 mos) 6-12 mos p<.0001 UDT: 83% / CDT: 20% 2 yrs (statistical test not done) UDT: 13% / CDT: 1.8% After 2 yrs Absent in both groups

CDT = contralateral ; mos = months ; NR = not reported; SD = standar deviation ; tbcx= tubular cross section ; UDT = undescended testis ; yr = year
* Data derived from a graph
¦Mean tubular fertility index (MTFI) and germ cell count (GC)

Table 36 Study results, testicular histology

Study (year) Period of operations	Study methods	Inclusion criteria	Outcomes	N patients (testes)	Mean age at surgery (range)	Characteristics (provided)	Fertility index observed (expected)
McAleer[42] (1995)	Prospective Compares age groups	Patients who underwent testicular biopsy No surgery	Fertility index*	226 patients ≤1yr: 38 1.5 yr: 17 2 yrs: 26 2-6 yrs: 49 > 6 yrs: 30	Mean age at biopsy: 3.6 yrs	Unilateral: 184 (81%)	**Unilateral, mean± SD (expected)** ≤1yr: 0.95±0.84 (2.1±0.32) 1.5 yr: 0.36±0.25 (1.78±0.32) 2 yrs: 0.3±0.2 (1.4±0.13) 2-6 yrs: 0.39±0.43 (1.95±0.61) > 6yrs: 0.53±1.07 (4.58±3.37) p<.05 **Bilateral, mean±SD (expected)** ≤1yr:1.015±0.83 (2.23±0.22) 1.5 yr: 0.7±0.54 (1.5±0.23) 2 yrs: 0.84±0.67 (1.39±0.62) 2-6 yrs: 0.33±0.42 (1.95±0.62) > 6yrs: 0.13±0.16 (4±1.55) P<.05 except 1.5yr
McAleer[42] (1995)	Prospective Compares UDT and CDT	Patients who underwent testicular biopsy No surgery	Fertility index*	226 patients ≤1yr: 38 1.5 yr: 17 2 yrs: 26 2-6 yrs: 49 > 6 yrs: 30	Mean age at biopsy: 3.6 yrs	Unilateral: 184 (81%)	**Unilateral, mean± SD (CDT)** ≤1yr: 0.78±0.77 (1.24±0.78) 1.5 yrs: 0.4±0.28 (1.4±0.66) 2 yrs: 0.37±0.2 (1.56±0.65) 2-6 yrs: 0.38±0.43 (1.64±0.75) > 6yrs: 0.43±0.58 (2.18±1.39)

CDT = contralateral descended testis ; mos = months ; UDT= undescended testis ; yr= year
* Fertility index observed: number of spermatogonia per tubule in 50 tubules examined at 300x magnification and averaging results.

2.2.6 Study results, diagnostic workup of impalpable testes

The tables below summarize the results of studies on the diagnostic workup of impalpable testes. In addition to study-specific comments, the age of the patients was always higher than the current indication of 1-2 years. In some studies adolescents and adults are included. Consideration needs to be given regarding the appropriateness of extrapolating these results to a population of 1-2 year-olds.

Additionally, tt is not clear if there comparisons were done against a gold standard. If open surgery can be considered as a gold standard than some of the comparisons are appropriate. However, if sensitivity/specificity is judged based on the results a non-gold standard such as ultrasound or MRI then the results may not be accurate. In most studies, it was not clear if the confirmation of the diagnosis by a second modality was done in a blinded fashion. This may also bias the results.

These factors should be taken into account when judging the applicability and relevance of these outcomes.

Table 37 Study results, systematic review, Diagnostic laparoscopy, ultrasound in non-palpable testis

	Study design	Inclusion criteria	# studies	Study characteristics	Diagnostic accuracy	Complications
Richardson[50] (2009)	Systematic review Diagnostic laparoscopy	NR	4 observational studies	NR	**Diagnostic laparoscopy** 99-100% Prevents abdominal explorations in 13-18% **Level III evidence***	0-3.2% (mostly intestinal injury)
Nijs[49] (2007)	Systematic review US vs. surgical exploration	NR	12 observational studies	Retrospective: 4 (33%) Prospective: 8 (67%)	**US vs. surgical exploration** 18-99%	NR

NR not reported ; US ultrasound
* Level III evidence as judged by the authors: descriptive

Table 38 Study results, comparative studies, MRI, ultrasound or laparoscopy in non-palpable testis

	Study design	# patients (testes)	Patient characteristics	Sensitivity	Specificity	False positives False negatives	Accuracy¦
Kanemoto[51] (2005) Evaluations: 1993-2002	Prospective Compares MRI alone with surgical exploration Diagnostic confirmations not blinded	40 (47)	Age: 1-12 yrs	**MRI vs. surgical expl.** 24/28 (86%)	**MRI vs. surgical expl.** 15/19 (79%)	**MRI vs. surgical expl.** False positives 4/19 (21%) False negatives 4/28 (14%)	**MRI vs. surgical expl.** 39/47 (85%)
Kanemoto[51] (2005) Evaluations: 1993-2002	Prospective Compares US alone with surgical exploration Diagnostic confirmations not blinded	46 (55)	Age: 1-12 yrs	**US vs. surgical expl.** 29/38 (76%)	**US vs. surgical expl.** 17/17 (100%)	**US vs. surgical expl.** False positives: 0 False negatives 9/38 (24%)	**US vs. surgical expl.** 46/55 (84%)
Kanemoto[51] (2005) Evaluations: 1993-2002	Prospective Compares US and MRI Diagnostic confirmations not blinded	29 (34)	Age: 1-12 yrs	NR	NR	**Both MRI and US** False positives US: 0 MRI: 3/34 (8.8%) False negatives US: 4/34 (11.8%) MRI: 3/34 (8.8%)	**Both MRI and US** US: 30/34 (88%) MRI: 28/34 (82%)

MRI = magnetic resonance imaging ; NR = not reported ; UDT = undescended testis ; US = ultrasound
*Evaluated by three pediatric urologists
¦ Accuracy: true positives + true negatives

Comments from authors (Kanemoto et al): US useful in identifying canalicular testes but not abdominal or atrophic testes. Inguinal testes not identified buy US were found to be moving from the abdominal to the inguinal position in surgical findings. MRI is more sensitive than US in localization of high testes especially abdominal. US more often used because real-time and repeated examinations can be done. [51]

Table 39 Study results, comparative studies, MRI, ultrasound or laparoscopy in non-palpable testis

	Study design	# patients (testes)	Patient characteristics	Sensitivity	Specificity	False positives False negatives	Accuracy
Wolverson[52] (1983) Evaluations: 1978-1980	Prospective Compares CT and high resolution US Diagnostic confirmations not blinded	20 (23)	3-23 yrs age < 5 yrs: 4 (20%) < 11 yrs: 7 (35%) Unilateral: 17 (85%)	US: 88% CT: 94%	US: 100% CT: 100%	False positives US: 0 CT: 0 False negatives US: 2/23 (8.7%) CT: 1/23 (4.3%)	US: 91% CT: 96%
Shah[53] (2006)	Prospective Compares US and laparoscopy	21	Children but age not specified	Comments from authors: 22/45 testes referred as impalpable were found to be palpable on examination by surgeon (importance of clinical examination)		NR	US accuracy as verified by laparoscopy: 4/21 (19%)
Nijs[49] (2007)	Prospective Compares US and surgical exploration Diagnostic confirmations not blinded	137 (156)	Age: 4 weeks-16.2 yrs	US:97% (viable inguinal) US: 48% (viable abdominal)		False positives 28% non-palpable by US appeared palpable in examination	**Authors** discuss lack of consensus on US usefulness
Sharifiaghdas[54] (2008) Evaluations: 2004-2006	Retrospective Compares US and diagnostic laparoscopy Diagnostic confirmations not blinded	76 (102)	Mean age: 15 yrs (1-39) Unilateral: 66%	**Authors comments:** true value of laparoscopy is in patients with blind-ending spermatic vessels and vasa deferentia proximal to the internal ring or high intra-abdominal testis Surgical management of high UDT is difficult.		Change in US findings after diagnostic laparoscopy 13/29 (44.8%) **No complications**	NR

CT = computed tomography ; HCG = human chorionic gonadotropin ; mos = months ; MRI = magnetic resonance imaging ; NR = not reported ; UDT = undescended testis ; US = ultrasound ; yrs = year

Table 40 Study results, comparative studies, MRI, ultrasound or laparoscopy in non-palpable testis

	Study design	# patients (testes)	Patient characteristics	Sensitivity	Specificity	False positives False negatives	Accuracy
Maghnie[55] (1994) Evaluations: 1989-1993	Prospective Compares US with surgical exploration Diagnostic confirmations not blinded	17 (22)	Age: 10 mos-14.5 yrs	NR	NR	US vs. surgery False positives 1/21 (4.8%) False negatives 4/21 (19%) – due to interference from adjacent structures that made localization of high testis impossible **Authors comments**: US very reliable for gonads at superficial and middle inguinal level but less reliable (limited value) for gonads at abdominal or upper-inguinal testis	US localized 16/21 (76%) testes
Maghnie[55] (1994) Evaluations: 1989-1993	Prospective Compares MRI with surgical exploration Diagnostic confirmations not blinded	17 (22)	Age: 10 mos-14.5 yrs	NR	NR	MRI vs. surgery False positives 0 False negatives 5/21 (24%) (atrophic testes) **Authors comments**: MRI appeared more sensitive than US to abdominal testes and was more specific in recognizing gonads having a Leydig's cell function	MRI localized 11/21 (52%) testes

CT computed tomography ; HCG human chorionic gonadotropin ; mos months ; MRI magnetic resonance imaging ; NR not reported ; UDT undescended testis ; US ultrasound ; yrs year

Table 41 Study results, comparative studies, MRI, ultrasound or laparoscopy in non-palpable testis

	Study design	# patients (testes)	Patient characteristics	Sensitivity	Specificity	False positives False negatives	Accuracy
Hederstrom[57] (1985)	Prospective US vs. surgery Diagnostic confirmations not blinded	60	Mean age: 6 yrs (3-12) Includes both non-palpable and palpable	NR	NR	**Author's comments:** The data suggests that US is a convenient screening method for small boys with non-palpable or UDT in the planning of an operation as long as the operation is restricted to the anteperitoneal region	53 (88%)
Moore[56] (1994)	Prospective Diagnostic laparoscopy vs. surgical exploration Diagnostic confirmations not blinded	104 (126)	Mean age: 34 mos (5mos-13yrs) Use of β-HCG stimulating test	NR	NR	Laparoscopy correctly identified the location of testes: 114/126 (90%) As verified by surgical exploration	NR
Sarihan[58] (1998)	Prospective US vs. MRI Diagnostic confirmations not blinded False negatives verified by surgery	20 testes	**Age not provided**	MRI: 78.6%	MRI: 100%	False positives MRI: 0 False negatives (Verified by surgery) MRI: 3 (15%) **MRI identified 13/20 (65%) testes** **US identified 8/28 (28.5%) testes**	NR

Table 42 Study results, comparative studies, MRI, ultrasound or laparoscopy in non-palpable testis

	Study design	# patients (testes)	Patient characteristics	Sensitivity	Specificity	False positives False negatives	Accuracy
Kier[60] (1988)	Prospective (MRI) MRI vs. surgery Diagnostic confirmations not blinded	14 (15)	Mean age: 2 yrs (11mos-5 yrs) < 2 yrs: 10 (71%)	MRI 5/8 (63%) (prospectively) 7/8 (88%) retrospectively	MRI 6/7 (86%) for absence (prospectively) 100% (retrospectively)	<u>False negatives</u> MRI vs. surgery: 3/8 (37.5%) 8 testes localized by surgery 5/8 (62.5%) localized by MRI <u>Absent testes by surgery</u> MRI vs. surgery: 6/7 (85.7%)	NR
Miyano[59] (1991)	Prospective MRI vs. surgery Diagnostic confirmations not blinded	17	Mean age: 2.7 yrs (1-5.3)			<u>False positives</u> Absence of testis: 2/8 (25%)	15/17 (88%) Absence: 6/6 (100%)

CT computed tomography ; HCG human chorionic gonadotropin ; mos months ; MRI magnetic resonance imaging ; NR not reported ; UDT undescended testis ; US ultrasound ; yrs year

Authors comments (Sarihan et al[58]): US and MRI are non-invasive techniques. US does not expose patients to radiation, does not require sedation of the patient and is cheaper than MRI. US was successful in identifying canalicular testes but not intraabdominal. US may be difficult in uncooperative children and patients with overlying gas filled bowel. For these reasons US has a limited role in the identification of impalpable undescended testes. MRI is non-invasive, non-ionizing and permits multiplanar images and has the potential for tissue characterization. MRI was successful in locating UDTs in very young children, it is more sensitive than US and CT in the localization of high testes and has an important role in the planning of the surgical strategy.

Authors comments (Kier et al[60]): MRI advantages: non-invasive, non-ionizing or intravascular contrast, allows multiplanar view of retroperitoneum

Table 43 Study results, comparative studies, MRI, ultrasound or laparoscopy in non-palpable testis

	Study design	# patients (testes)	Patient characteristics	Sensitivity	Specificity	False positives False negatives	Accuracy
Zobel[62] (1990)	Prospective MRI vs. surgery	20 (23)	Ages 5-23 years	MRI 88%	MRI 100%	MRI False positives: 0 False negatives: 2 (10%) **Author's comments:** MRI appears to be the most effective to locate an abdominal testis.	MRI 90%
Malone[61] (1985)	Prospective US vs. laparoscopy confirmed by surgery; Diagnostic confirmation blinded	11 (14)	Mean age: 6 yrs (3-12)	NR	NR	Accurate location of non-absent testes Laparoscopy: 12/12 (100%) US: 2/12 (17%)	NR
Weiss[63] (1986)	Prospective US vs. surgery	21 non-palpable testes	Mean age: 6 yrs (10 mos-39 yrs)* Intraabdominal: 3 (37.5%) Inguinal: 5 (62.5%)	NR	NR	US Detected 1/8 (12.5%) non-palpable testes	NR
Siemer[64] (2000)	Prospective MRI vs. surgery	29	Mean age: 4.5 yrs (1-15)	NR	NR	Demonstrable testes False positives: 0/4 Correct identification: 17/25 (68%) Non-demonstrable testes False negatives : 8/25 (32%) Correct negative : 4/4 (100%)	NR
Siemer[64] (2000)	Prospective laparoscopy vs. surgery (testes not demonstrated by MRI)	12	Mean age: 4.5 yrs (1-15)	NR	NR	Demonstrable testes False positives: 2/4 (50%) Correct identification: 8/8 (100%) Non-demonstrable testes False negatives : 0/8 Correct negative : 2/4 (50%)	NR

CT = computed tomography ; HCG = human chorionic gonadotropin ; mos months ; MRI = magnetic resonance imaging ; NR = not reported ; UDT = undescended testis ; US = ultrasound ; yrs = year

* Mean age in the whole group includes palpable

Authors' comments (Siemer et al [64]): From literature: advantages of laparoscopy: in the same anesthesia, open exploration is possible, sensitivity 90-100%, specificity: 80-100%, false negatives: 0, costs: single investment for equipment, minimally invasive.
From study results: when laparoscopy is not available, MRI, which is the most sensitive radiological method is advised. If a testis is detected by MRI this finding has a high accuracy rate and orchidopexy can be planned. If testes not seen on MRI further diagnostic tests are necessary due to high false-negative rate.

3 QUALITY APPRAISAL OF STUDIES INCLUDED IN THE REPORT

The assessment of the quality of publications included in the report was adapted from Australian guidelines.[4] Quality of RCTs was also assessed according to the Jadad criteria.[3] For non-comparative studies the study characteristics and study design are provided due to the absence of standardized study evaluation criteria.

3.1 Quality appraisal of studies on orchidopexy

Table 44 Quality appraisal of systematic reviews (orchidopexy)

Study	Outcome	Appropriate search strategy?	Study Design No. studies	Study quality assessment performed?	Study charact. Appropriately summarized?	Methods for pooling data appropriate?	Sources of heterogeneit explored?	F-up	Statistical precision	Effect size	Clinical relevance
Esposito[10] (2008)	Surgery success	Not provided	Observational 18 studies*	No	No	Not pooled	No	NR	NA	NA	Outcome relevant however, atrophy or other complications
Taran[11] (2006)	Surgery success	Not provided	Observational 24 studies*	No	No	Not pooled	No	NR	NA	NA	
Docimo[1] (1995)	Surgery success	Not provided	Observational 64 studies	No	No	Not weighted	No other than	NR	NA	NA	

						according to sample size. Stratified according to certain study/patient charatct.§	subgroup analyses§				not reported Atrophy may be inferred by no success? Includes orchidopexy done after 2 years of age

Diff difference ; NA not applicable ; NR not reported ; RCT randomized controlled trial
*Includes one systematic review
§ Subgroups: study publication year (<1995, > 1995), mean patient age (< 6years, > 6 years), follow-up time (< 6 months, > 6 months), testis location

Table 45 Quality appraisal of RCTs (orchidopexy)

Study	Described as rdz?	Rdz method described? Appropriate?	Double-blind?	Double-blind method described? Appropriate?	Withdrawals descript?	Comparability btw study groups	F-up	Statistical precision	Effect size	Clinical relevance	Total Jadad score
Comparison: surgery at different age											
Kollin[15] **Jadad Score**	Yes 1	No 0	No 0	N/A 0	No, not clear 0	Not clear, information not provided (location etc.) N=77	Up to 4 yrs Loss f-up possible not clear	Small p-values but wide CI in each group	Diff. in testicular vol. 0.12ml.	Not clear No complic.	1/5
Laparoscopy vs. orchidopexy											
Abolyosr[1][2] **Jadad Score**	Yes 1	No 0	No 0	N/A 0	No, N. provided not reasons 0	Stratified according to location Small N, 41	Up to 31 mos	Not provided	Same rate of success	Testis position – relevant ? Complic.	1/5

Hormone therapy vs. no hormone before orchidopexy											
Jallouli[18] **Jadad Score**	Yes 1	No 0	No 0	N/A 0	No 0	V. small N, 24, esp. for subgroup analyses Specific location	0	Small p-value but overlapping CIs	Diff. 0.4 in fertility index	Fertility index ? No complic.	1/5
Schwentner[19] **Jadad Score**	Yes 1	No 0	No 0	N/A 0	No 0	Not clear Small N=42 (21 / 21), esp. subgroup analyses	0	Small p-value but overlapping CIs	Diff. 0.4 in # cells	# spermatogonia/tbcx ?	1/5

Table 46 Quality appraisal, non-randomized comparative studies (orchidopexy)

Study	Selection Intervention	Selection Controls	N (intervention/control)	Group comparability	Control for diff. charact.	Outcome measurement	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance
Comparison: age at orchidopexy										
Park[16]	Prospective Divided into 4 age groups	-	65 (20 / 30 / 7 / 8)	No Small N espec. In some groups Inguinal location	No	Well described Assessor blinded to patient group	0	v. small p-value but overlapping CIs	0.2-0.4 diff in fertility index	Not clear
Michikawa[17]	Retrospective Divided into 2 age groups (< 2yrs , > 2 yrs)	Retrospective	23 (13 / 10)	Testes location similar	No	Testicular volume, risk of abnormalities Well described Assessor blinded to patient group	5 years 9 not in 5-yr analysis	Not statistically significant	25% vs. 83% diff in abnormalities risk in <2yrs vs. > 2 yrs	Not clear
Single prescrotal incision vs. traditional inguinal approach										
Al-Mandil[14]	Retrospective	Age-matched controls,	103 (53 / 47)	Table with patient demographic	Age only	Complications Retrospective	6-42 mos N/A losses f-up	Not statistically significant	Similar results	Relevant

		retrospect. identified		Palpable testes Location similar						
Laparoscopy vs. inguinal exploration (non-palpable)										
Chandrasekharam[13]	Prospective	Age-matched controls	27 (13 / 14)	Table with patient demographic Non-palpable Location similar	Age only	Blinding of assessment not mentioned	4-6 wks Loss: 0	Not statistically significant	Similar results	Relevant
Hormone therapy vs. no hormone before orchidopexy										
Hadziselimovic[22]	Prospective (presumed)	Not clear Not clear if hormone group was operated on	65 (32 / 33)	Not provided	No	Biopsies evaluated in a blinded fashion	2 mos loss- f-up not clear	v. small p-value but overlapping CIs	100 ng/dl testosterone level 35% absolute diff % pts >0.1 ad/tbcx	Relevant ?
Hormone therapy vs. no hormone after orchidopexy										
Hadziselimovic[20]	Prospective	Retrospective selection	15 vs. 181 controls	Testis location mostly inguinal or external ring <0.2 germ cells/tbcx Small n intervention	Age only	Measurement approx. 15 yrs after intervention Complications included	15 yrs	v. small p-value (sperm count)	Diff in sperm conc./ejaculate: 90 x10^6 Normal morphology: 11% absolute diff	Relevant ?
Hadziselimovic[21]	Retrospective (presumed)	Retrospective	33 (10 / 23)	V. small N No mention of comparability	No	Measurement approx. 12 yrs after intervention	12 yrs	Small p-value	T. sperm count: 23 diff. Normal sperm forms: 16% diff % motile sperm 30% diff	Relevant ?

Table 47 Study design, observational non-comparative studies (orchidopexy)

Study	Study methods	No. testes / patients	Outcomes	Outcome measurement blinded?	F-up Patient attrition	Clinical relevance of outcome
Lintula[65]	Retrospective	34	Surgical success and complications	N/A (retrospective)	12 months 2 losses f-up	Relevant Mean age: 2.5 years
Palmer[66]	Retrospective	64	Surgical success and complications	N/A (retrospective)	4 months 0 losses f-up	Relevant Mean age: 10 months
Kaye[67]	Retrospective	42	Surgical success and complications	N/A (retrospective)	12 months 0 losses f-up	Relevant Mean age: 9 months
Yucel[68]	Retrospective	46	Surgical success and complications	N/A (retrospective)	Up to 25 months 4 losses f-up	Relevant Mean age: 12-35 months
Robertson[69]	Retrospective	25	Surgical success and complications	N/A (retrospective)	18 months 7 losses f-up	Relevant Mean age: 36 months
Horasanli[70]	Prospective	24	Surgical success and complications	One surgeon performed the post-surgery evaluations	12 months 0 losses f-up	Relevant Mean age: 2 years
Takahashi[71]	Retrospective	49	Surgical success and complications	N/A (retrospective)	39 months (median) 0 losses f-up	Relevant Mean age: 3.3 years
Dayanc[72]	Prospective	204	Surgical success and complications	Not reported	29 months (mean) 25 losses f-up	Relevant Mean age: 2.2 years
He[73]	Prospective	103	Surgical success and complications	Not reported	12 months 0 losse f-up	Relevant Mean age: 17 months
Al-Saied[74]	Prospective	75	Surgical success and complications	Not reported	12 months 0 losses f-up	Relevant Mean age: 13 months

f-up follow-up

3.2 Quality appraisal of studies on hormone treatment of cryptorchidism

Table 48 Quality appraisal, meta-analyses (hormone treatment)

Study	Comparators Outcome	Appropriate search strategy?	Study Design No. studies	Study quality assessment performed	Study charact. appropriately summarized ?	Methods for pooling data appropriate?	Sources of heterogeneity explored?	F-up	Statistical precision	Effect size	Clinical relevance
Henna[23] (2004)	hCG vs. GnRH Complete testicular descent	According to Cochrane methods*	3 RCTs (up to June 03)	Yes, moder. bias risk, not proper allocation concealment	No	Fixed-effect model (Peto)	Not mentioned	NR	Narrow CI on fixed-effects model, heterogeneity not discussed	Small (7% ARR)	Relevant but long-term relapses and complications not reported Heterogeneity in studies and patient characteristics not discussed
Henna[23] (2004)	GnRH vs. placebo Complete testicular descent	As above	9 RCTs (up to June 03)	Yes, rdz process described in 1 RCT, no drop-outs	No	Fixed-effect model (Peto)	Not mentioned	NR	Narrow CI on fixed-effects model, heterogen	Small (14% ARR)	As above

									eity not discussed		
Pyorala[2][4] (1995)	LHRH vs. placebo Testes descent	Yes*	9 RCTs (up to 1990) 4 RCTs (excluding retractile testes)	No	No	Fixed-effects	Subgroup analyses**, Some include retractile testes	NR	Narrow CI on fixed-effects model, heterogeneity not discussed	Small (15-20% ARR) entire group Smaller diff excluding retractile testes	As above
Ong[25] (2005)	Difference between hormones vs. hormones or placebo	Not described	6 RCTs (1991-2003)	yes	No	Not pooled	Some subgroup analyses	NR	NR	0-35% diff success rate	Relevant, failure reported in some, not complications Limitations as above

ARR = absolute risk reduction ; Diff = difference ; moder = moderate ; GnRH = gonadotropin-releasing hormone HCG = human chorionic gonadotropin ; IM = intramuscular ; LHRH = luteinizing hormone releasing NR not reported ; RCT = randomized controlled trial
*Search terms not provided
** Few subgroup analyses conducted, some included non-randomized studies

3.3 Characteristics of observational studies and systematic reviews of the effects of orchidopexy on fertility

Table 49 Quality appraisal, systematic reviews of observational studies (effects on fertility)

Study	Outcome	Appropriate search strategy?	Study Design No. studies	Study quality assessment performed?	Study charact. appropriately summarized?	Methods for pooling data appropriate?	Sources of heterogeneit explored?	F-up	Statistical precision	Effect size	Clinical relevance
Chilvers [29] (1986)	Sperm concentration (oligospermia, azoospermia)	Not described	24 observational studies	Large variation in results between studies	Information not provided	Information not provided	No	NR	N/A	N/A - not compar ative	Outcome is relevant, but population from individual not described studies therefore it is difficult to assess if the population is similar to the one of interest

N/A = not applicable; NR = not reported

Table 50 Study characteristics, observational non-comparative studies (effects on fertility)

Study	Study methods	No. patients (testes)	Outcomes	Patient attrition (non-participation rate)	Effect size	Clinical relevance of outcome
Hadziselimovic [26] (2006)	Prospective (adult measurements) Retrospective (surgery information) Results stratified by age-group (post-hoc)	218 (255)	Infertility Sperm count Ad spermatogonia count Comparability of different age groups not assessed	218/231 (94%) – not clear if all 231 patients were contacted	Difference between age groups statistically significant, however age-group breakdown defined post-hoc, possibly based on statistical significance	Relevant: infertility Association between cell count and fertility does not seem to be established Age group stratification breakdown (< 3yrs vs. > 8 yrs or < 3yrs vs. > 4yrs at surgery) defined post-hoc after looking at results – potential for bias Comparability of different age groups not assessed
Coughlin[27] (1999)	Prospective Results stratified by age-group	84	Hormones (FSH, testosterone) Sperm density, inhibin B	NR	No difference between age groups	Association between outcomes and fertility does not seem to be established Patients from a male fertility study, which could result in selection bias although the authors do not specify if study participation was associated with infertility Comparability of different age groups not assessed

Table 50 cont. Study design, observational non-comparative studies (effects on fertility)

Study	Study methods	No. patients (testes)	Outcomes	Patient attrition (non-participation rate)	Effect size	Clinical relevance of outcome
Taskinen[30] (1997)	Prospective Retrospective (surgery data) Results stratified by age-group	73	Testicular volume	73 out of 149 patients contacted (49%) responded	No difference between age groups	Association between testicular volume and fertility does not seem to be established All patients with bilateral cryptorchidism Comparability of different age groups not assessed
Lee[31] (2002)	Prospective Men with orchidopexy compared to age-matched controls Correlation between testosterone level and age at orchidopexy evaluated, method not provided	106 orchidopexy 52 controls	Testosterone levels	NR	No difference between age groups	Association between testosterone levels and fertility does not seem to be established. Statistical method of analysis not provided in details Comparability of different age groups not assessed
Lee[32] (2001)	Prospective Retrospective (surgery data) Results stratified by age-group	166	Paternity	No patient loss	No difference between age groups	Relevant outcome

Table 50 cont. Study design, observational non-comparative studies (effects on fertility)

Study	Study methods	No. patients (testes)	Outcomes	Patient attrition (non-participation rate)	Effect size	Clinical relevance of outcome
Lee[33] (1995)	Prospective questionnaire survey Retrospective (surgery data) Results stratified by age-group	363 orchidopexy 336 controls	Paternity	NR	No difference between age groups	Relevant outcome Comparability of different age groups not assessed Small numbers in each group reduce precision in results
Miller[34] (2001)	Prospective questionnaire survey Retrospective (surgery data)	359 orchidopexy 443 controls	Paternity	No patient loss	No difference between age groups	Relevant outcome All patients with unilateral cryptorchidism Comparability of different age groups not assessed
Engeler[28] (2000)	Prospective Results stratified by age-group	35 (fertility) 24 (semen analysis)	Sperm concentration Sperm motility and normal forms	35/70 (50%) – reason for exclusion not provided 24 patients agreed to semen analysis	Different rates of fertility among age groups, statistical significance not assessed	Association between outcomes and fertility does not seem to be established All patients with bilateral UDT Comparability of different age groups not assessed
Cendron[35] (1989)	Retrospective Results stratified by age-group	37 patients	Paternity	37 out of 40 patients agreed to participate	No difference between age groups	Relevant outcome Comparability of different age groups not assessed Small numbers in each group reduce precision in results

f-up = follow-up ; FSH = follicle-stimulating hormone ; NR = not reported ; UDT = undescended testis

3.4 Quality appraisal of the effects of orchidopexy on malignancy

Table 51 Quality appraisal of systematic reviews and meta-analysis (effects on malignancy)

Study	Outcome	Appropriate search strategy?	Study Design No. studies	Study quality assessment performed	Study charact. Appropriately summarized?	Methods for pooling data appropriate?	Sources of heterogeneity explored?	F-up	Statistical precision	Effect size	Clinical relevance
Wood[45] (2009)	Testicular cancer	Yes	Observational studies 9 Cohort or case-controls 2 meta-analyses 4 others	No	Partially	N/A (did not pool results)	No	2-35 yrs	N/A	RRs 2.8-8 vs. general population	Relevant outcome, however, included patients with cryptorchidism, which may encompass different diagnoses other than congenital UDT with different risks of testicular cancer jeopardizes the interpretability of results
Tuazon[44] (2008)	Testicular cancer	Yes	Walsh et al. plus 2 observational studies	No	Partially	Pools data from diff. obs. studies may have patients with diff characteristic, outcome measurement, adjustment for confounders	No	NR	Yes	RRs 2.7 (1.1 , 6.3) Older vs. younger age group	
Walsh[43] (2007) Meta-analysis	Testicular cancer	Yes	2 cohort 3 case-controls	No	Partially		No	NR	Very wide CI p=0.1	RR 3.4 (0.7 , 17.7)	

CI = confidence interval ; Diff = difference ; N/A = not applicable ; NR = not reported ; obs = observational ; RCT = randomized controlled trial ; UDT = undescended testes
*Includes one systematic review

Table 52 Quality appraisal of observational studies (effects on malignancy)

Study	Selection Cohort	N (N. cases)	Control for patient characteristics, confounding	Outcome measurement unbiased ?	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance
Pettersson[46] (2007)	According to ICD codes National discharge and cancer databases	16,983 (56 cases)	Not all, only period of surgery and f-up	No, cancer registry (ICD codes)	Censoring for patients who left the cohort	Relatively wide CIs in some age groups, small # cases, i.e., 5 in < 6yrs group	RR 2- 6.2 depending on age group at orchidopexy vs. general population	Relevant outcome, however unknown confounders associated with calendar time may be present. Inclusion of acquired and congenital UDT may affect outcome and may jeopardize interpretability of results. Age subgroup 0-6 yrs at surgery not stratified further.
Myrup[48] (2007)	According to ICD codes National discharge and cancer databases	21,488 (110 cases)	Not clear may be similar to Petterson et al.	No, cancer registry (ICD codes)	Attrition not described	Relatively wide CIs in some age groups, small # cases i.e., 9 in < 6yrs group	RR 3.2- 5.5 depending on age group at orchidopexy vs. general population	
Dusek[47] (2008)	Cases: TGCC cases treated at 2 hospitals Controls: healthy men recruited in the same hospitals	356 cases 317 controls	Multivariate logistic regression includes statistically significant variables	No, ICD codes	Patient refusal to participate not described	Relatively narrow CIs, however, orchidopexy not in multivariate analysis	Orchidopexy not included in multivariate analysis Univariate analysis: OR: 5.2	Effect of orchidopexy at < 5yrs age only included in univariate analysis therefore no estimate adjusting for other predictors.

CI confidence interval ; f-up follow-up ; ICD International Statistical Classification of Diseases and Related Health Problems ; RR risk ratio ; UDT undescended testis

3.5 Quality appraisal of the diagnoses of impalpable testes

As previously discussed, some factors should be considered when judging the applicability of the results of these studies to the population of interest such as age of participants, possible lack of use of gold-standard, and blinding of examiners to previous results with different diagnostic modalities.

Table 53 Quality appraisal of systematic reviews (diagnosis of impalpable testes)

Study	Outcome / comparator	Appropriate search strategy?	Study Design No. studies	Study quality assessment performed?	Study charact Appropriately summarized?	Methods for pooling data appropriate?	Sources of heterogeneit explored?	F-up	Statistical precision	Effect size	Clinical relevance
Richardson[50] (2009)	Diagnostic accuracy Laparoscopy	NR	4 observational studies	No	No	N/A	No	N/A	NR	NR	Not clear what was the reference diagnostic test used
Nijs[49] (2007)	Diagnostic accuracy US vs. surgery	NR	12 observational studies	No	No	N/A	No	N/A	NR	NR	Wide variation of study results not discussed

N/A = not applicable ; NR = not reported ; US = ultrasound

Table 54 Quality appraisal of observational studies (diagnosis of impalpable testes)

Study	Outcome / comparator	Selection of participants	N. of patients (testes)	Group comparability	Control for diff. charact.	Outcome measurement	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance (see age comment in 1st page)
Moore[56] (1994)	False positives, false negatives Laparoscopy vs. surgery	Patients with non-palpable testes Mean age: 34 mos	104 (126)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Relevant if surgery is considered the gold standard
Kanemoto [51] (2005)	Specificity, sensitivity MRI or US vs. surgery, US vs. MRI	Patients with non-palpable testes Age 1-12 yrs	86 (102)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Relevant if surgery is considered the gold standard.
Wolverson [52] (1983)	Specificity, sensitivity CT vs. US	Patients with non-palpable testes Age: 3-23 yrs	20 (23)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Not relevant unless one of the modalities can be considered the gold standard
Shah[53] (2006)	Accuracy US vs. laparoscopy	Patients with non-palpable testes Age NR	21	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Not relevant unless one of the modalities can be considered the gold standard
Sharifiaghdas[54] (2008)	False positives and false negatives US vs. laparoscopy	Patients with non-palpable testes Mean age: 15 yrs (1-39)	76 (102)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Not relevant unless one of the modalities can be considered the gold standard

CT = computed tomography ; mos = months ; MRI = magnetic resonance imaging ; N/A = not applicable ; NR = not reported ; US = ultrasound

Table 55 Quality appraisal of observational studies, (diagnosis of impalpable testes)

Study	Outcome / comparator	Selection of participants	N. of patients (testes)	Group comparability	Control for diff. charact.	Outcome measurement	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance (see age comment in 1st page)
Nijs[49] (2007)	Accuracy US vs. laparoscopy	Patients with non-palpable testes Age: 4 weeks-16.2 yrs	137 (156)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Not relevant unless one of the modalities can be considered the gold standard
Maghnie[55]	False positives, false negatives, accuracy US or MRI vs. surgery	Patients with non-palpable testes Age: 10 mos-14.5 yrs	17 (22)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Relevant if surgery is considered the gold standard
Hederstrom[57] (1985)	Accuracy US vs. surgery	Patients with impalpable testes but may include palpable testes Mean age: 6 yrs (3-12)	60	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	

Table 56 Quality appraisal of observational studies (diagnosis of impalpable testes)

Study	Outcome / comparator	Selection of participants	N. of patients (testes)	Group comparability	Control for diff. charact.	Outcome measurement	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance (see age comment in 1st page)
Sarihan[58] (1998)	Prospective US vs. MRI Diagnostic confirmations not blinded False negatives verified by surgery	Patients with impalpable testes Age not provided	20 testes	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Not relevant unless one of the modalities can be considered the gold standard
Kier[60] (1988)	Sensitivity, specificity, false negatives MRI vs. surgery	Patients with impalpable testes Mean age: 2 yrs (11mos-5 yrs)	14 (15)	Patients used as their own control	N/A	Well described Diagnostic confirmation not blinded especially problematic when retrospective MRI evaluations were done	N/A	NR	N/A	Relevant if surgery is considered the gold standard However, prospective results should be considered since authors also presented retrospective MRI results after knowing the results of surgery
Miyano[59] (199)	Accuracy, false positives MRI vs. surgery	Patients with impalpable testes	17 Mean age: 2.7 yrs (1-5.3)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Relevant if surgery is considered the gold standard

CT = computed tomography ; MRI = magnetic resonance imaging ; N/A = not applicable ; NR = not reported ; US = ultrasound

Table 57 Quality appraisal of observational studies (diagnosis of impalpable testes)

Study	Outcome / comparator	Selection of participants	N. of patients (testes)	Group comparability	Control for diff. charact.	Outcome measurement	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance (see age comment in 1st page)
Zobel (1990)	Sensitivity, specificity, false negatives MRI vs. surgery	Patients with impalpable testes Age 5-23 yrs	20 (23)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Relevant if surgery is considered the gold standard
Malone (1985)	Accurate location of non-absent testes	Patients with impalpable testes Mean age: 6 yrs	11 (14)	Patients used as their own control	N/A	Technique not described	N/A	NR	N/A	Relevant if surgery is considered the gold standard
Weiss (1986)	Accurate location of non-palpable testes	Patients with impalpable testes Mean age: 6 yrs	21	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Relevant if surgery is considered the gold standard
Siemer (2000)	Accurate location, false negatives	Patients with impalpable testes Mean age: 4.5 yrs	29 (MRI) 12 (Laparoscopy)	Patients used as their own control	N/A	Well described but diagnostic confirmation not blinded	N/A	NR	N/A	Relevant if surgery is considered the gold standard

CT = computed tomography ; MRI = magnetic resonance imaging ; N/A = not applicable ; NR = not reported ; US = ultrasound

3.6 Quality appraisal of testicular histology studies

Table 58 Quality appraisal of observational studies (testicular histology)

Study	Selection of participants	N. of patients (testes)	Group comparability	Control for diff. charact.	Outcome measurement	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance
Hadziselimovic[39] (2007)	Patients with unilateral orchidopexy Results were divided by age grop	218 (255)	Not provided	Only age	Well described	N/A	Statistically significant	Diff. in sperm count/ejaculate : approx. $80x10^6$	To be confirmed
Hadziselimovic[37] (2001)	Patients with unilateral orchidopexy and testicular biopsy Results were divided by age grop	31	Not provided	Only age	NR	N/A	Statistically significant	Diff in mean germ cell count/tbcx: approx. 4.5	To be confirmed
Hadziselimovic[38] (2001)	Patients with unilateral orchidopexy and testicular biopsy before 2 years of age Results were divided by age grop	27	Not provided	Only age	NR	N/A	Statistically significant	Diff in mean germ cell count/tbcx: approx. 4.7	To be confirmed
Hadziselimovic[36] (2004)	Cryptorchid patients with testicular biopsy Results were divided by age grop	125 biopsies	Not provided	Only age	NR	N/A	Statistically significant	Small difference in Ad spermatogonia /tbcx	To be confirmed

Diff = difference ; N/A = not applicable ; NR = not reported ; tbcx = tubular cross section

Table 58 cont. Quality appraisal, testicular histology studies

Study	Selection of participants	N. of patients (testes)	Group comparability	Control for diff. charact.	Outcome measurement	F-up Patient attrition	Statistical precision	Effect size	Clinical relevance
Huff[40] (1993)	Patients with orchidopexy and testicular biopsy Results were divided by age grop	399 biopsies (UDT) 356 biopsies (CDT)	Not provided	Only age	Well described	N/A	Statistically significant in age groups > 12 months	Small but consistent difference in germ cell count	To be confirmed
Huff[41] (1989)	Patients with orchidopexy and testicular biopsy Results were divided by age grop	232 (UDT) 195 (CDT)	Not provided	Only age	Well described	N/A	Statistically significant	Differences shown in graphs	To be confirmed
Park[16] (2007)	Patients with orchidopexy and testicular biopsy Results were divided by age grop	65 testes	Not provided	Only age	Well described	N/A	Statistically significant	Small but consistent difference in histology measures	To be confirmed
McAleer[42] (1995)	Patients with orchidopexy and testicular biopsy Results were divided by age grop	226 patients	Not provided	Only age	Well described	N/A	Statistically significant	Small but consistent difference in fertility index	To be confirmed

CDT = contralateral descended testis ; Diff = difference ; N/A = not applicable ; NR = not reported ; tbcx= tubular cross section ; UDT = undescended testis

4 Evidence tables

Table 59 Evidence table, orchidopexy

Indication	Study design	Study quality	Consistency	Directness (population, interventions and outcomes reflect study question)	Overall rating*
Age at orchidopexy (open surgery) Palpable testes	1 RCT 1 observational study	Small sample sizes, comparability between groups not clear Inclusion criteria not provided F-up; up to 4 yrs (RCT) Risk of bias	Results seem to be better with lower age however numerical comparability difficult Imprecise results	Not clear Relevance of outcomes ? Relevance of study population and interventions ? Complications (atrophy etc.) not reported	**Level of evidence** 1 minus (RCT with high risk of bias) **Strength of recommendations** Not applicable¦
Laparoscopy vs. orchidopexy Non-palpable testes Direct or 2nd part of 2-stage Fowler Stephens	1 RCT	Small sample size Comparability between study groups not clear, stratified according to age Inclusion criteria not provided F-up: up to 31 mos Risk of bias	N/A (1 study)	Mean age: 5.3 yrs (applicable ?) Outcomes seem to be appropriate (success, atrophy)	**Level of evidence** 1 minus (RCT with high risk of bias) **Strength of recommendations** Not applicable¦
Single prescrotal incision vs. inguinal approach Non-palpable testes	1 observational study	Retrospectively selected patients in two groups 103 patients Testes location similar between groups Inclusion criteria not provided F-up 6-42 mos	N/A (1 study)	Mean age: 5yrs Outcomes relevant? (complications of surgery)	**Level of evidence** 2 minus (high risk of bias) **Strength of recommendations** Not applicable¦

		Risk of bias			
Laparoscopy vs. inguinal exploration Non-palpable	1 observational study	Very small sample (n=27) Short f-up: 4-6 wks Inclusion criteria not provided Testis location similar Risk of bias	N/A (1 study)	Mean age: 3 yrs Outcomes relevant (success and atrophy)	**Level of evidence** 2 minus (high risk of bias) **Strength of recommendations** Not applicable¦

*Overall rating according to the GRADE working group[5,6]
¦ Strength of recommendation for level of evidence 1 minus or 2 minus not defined

Table 60 Evidence table, Hormone therapy adjuvant to orchidopexy

Indication	Study design	Study quality	Consistency	Directness (population, interventions and outcomes reflect study question)	Overall rating*
Hormone therapy vs. no hormone before surgery Palpable testes	2 RCTs 1 observational study	Small study sizes Inclusion criteria not provided Comparability between study groups not clear Short f-up: 0-2 mos Imprecise results Risk of bias	Use of hormone therapy seems to yield better results than no therapy before orchidopexy. However, imprecise results and clinically relevance of type of outcome and effect size make interpretation difficult	Lack of reporting of inclusion criteria in 2 studies do not permit applicability to population of interest. May include retractile testes. Clinical significance of types of outcomes and effect size not clear (fertility index, # cells) Treatment complications not reported	**Level of evidence** 1 minus (RCT with high risk of bias) **Strength of recommendations** Not applicable¦ **Modifiers** Lack of clinical significance of outcomes Lack of evaluation of treatment complications Both factors reduce the importance of the evidence Especially since data

					indicates that more harm is caused in children < 4yrs.
Hormone therapy vs. no hormone after orchidopexy Palpable in 1 study, not clear in the other	2 observational studies	Small study sizes Retrospective No mention of inclusion criteria or comparability of groups in 1 study F-up: 12-15 yrs after treatment Risk of bias	Use of hormone therapy seems to yield better results than no therapy. However, imprecise results and clinically relevance of type of outcome and effect size make interpretation difficult	Lack of reporting of inclusion criteria in 2 studies do not permit applicability to population of interest. Clinical significance of types of outcomes and effect size not clear (testicular volume, spermogram) Treatment complications not reported	**Level of evidence** 2 minus (high risk of bias) **Strength of recommendations** Not applicable¦ **Modifiers** See above for treatment before surgery.

*Overall rating according to the GRADE working group[5,6]

¦ Strength of recommendation for level of evidence 1 minus or 2 minus not defined

Table 61 Evidence table, Hormone therapy

Indication	Study design	Study quality	Consistency	Directness (population, interventions and outcomes reflect study question)	Overall rating*
Hormone treatment for cryptorchidism Not specified if palpable testis or not	2 Meta-analysis of RCTs (4-9 RCTs each) 1 Systematic review of RCTs and non-randomized studies	Large number of trials included Inconsistent assessment of individual study quality (1 author reported moderate bias risk due to not proper allocation) Characteristics of patients in individual studies not provided therefore not clear if studies are similar May have included retractile testes Heterogeneity not discussed	Consistency in magnitude of results although different hormone treatments were used in studies	Difficult to assess population appropriateness Outcome seems relevant (complete descent), however relapse may occur in ¼ of patients (according to 1 study in systematic review) and this outcome was not included in meta-analyses Risk difference with treatment is low, ARR 7%-15% Treatment complications not evaluated	**Level of evidence** 1minus (meta-analysis with high risk of bias) or 1+ (well conducted meta-analysis low risk of bias). Low risk of bias not likely given the comments on this table. **Strength of evidence** B (if 1+ is used) **Modifiers** Treatment complications¶ and relapses not evaluated – reduces importance of evidence More harm in children < 4yrs

ARR absolute risk reduction

*Overall rating according to the GRADE working group[5,6]

¶ Treatment complications with hormonal treatment: repeated pain at site of injection, growth of the penis, pubic hair, pain in the groin, erection pain, behavioral problems, temporary inflammatory changes in the testes, germ cell apoptosis, and reduction in the number of germ cells and the sizes of the testes in adulthood (Nordic). A study showed adverse effects may be age-dependant, with most harm in the 1-3 years age group (Nordic).

¦ Strength of recommendation for level of evidence 1 minus or 2 minus not defined

Table 62 Evidence table, diagnostic workup of impalpable testes

Indication	Study design	Study quality	Consistency	Directness (population, interventions and outcomes reflect study question)	Overall rating*
Diagnostic workup of impalpable testes	2 systematic reviews 15 observational study Studies compared either MRI, US or laparoscopy to another diagnostic modality, including open surgery	In most studies the diagnostic results of MRI, US or laparoscopy were compared to open surgery. **If open surgery can be considered a gold standard then the comparison is appropriate. Otherwise or in cases where the diagnostic modalities were compared among themselves without a gold standard the interpretability is jeopardized** **It also seems that in most cases the diagnosis confirmation was not done in a blinded fashion**	The accuracy, specificity and sensitivity of each modality was not consistent across studies. Some authors mentioned that the location of the testis or other patient characteristics may affect the diagnosis rate and may be in part responsible for the inconsistency. Patient heterogeneity and imprecision due to sample size may also contribute to inconsistency	To be confirmed: It seems that most patients included in the studies are above the age of 1-2 years. Some studies include adolescents and adults. If this affects outcomes and cannot be extrapolated to 1-2 year-olds than directness is compromised. Comments about possible lack of gold standard when judging the applicability of the evidence should also be considered.	**Level of evidence** 2 minus (it could be classified as 2+ if we could classify the studies as well conducted case-control or cohort studies, and I'm not sure if this is appropriate especially given comments about gold standard and blinding) **Strength of recommendations** Not applicable¦ or C (in case level of evidence=2+)

MRI magnetic resonance imaging ; US ultrasound
*Overall rating according to the GRADE working group[5,6]
¦ Strength of recommendation for level of evidence 1 minus or 2 minus not defined

Table 63 Evidence table, evaluation of testicular histology according to age

Indication	Study design	Study quality	Consistency	Directness (population, interventions and outcomes reflect study question)	Overall rating*
Evaluation of testicular histology according to age	8 observational studies	Studies generally stratified the patients into age group or compared results of undescended and descended testis. Other than age it is difficult to assess if the groups are comparable.	Results in general showed that after age 1-2 years, undescended testes have less germ cells compared to either contralateral descenced testes or controls	Study population seems to be similar to population of interest, however, baseline characteristics not provided. Outcome results seem consistent however relevance needs to be confirmed	**Level of evidence** 2 minus (it could be classified as 2+ if we could classify the studies as well conducted case-control or cohort studies, and I'm not sure if this is appropriate) **Strength of recommendations** Not applicable¦ or C (in case level of evidence=2+)

*Overall rating according to the GRADE working group[5,6]
¦ Strength of recommendation for level of evidence 1 minus or 2 minus not defined

Table 64 Evidence table, effects of orchidopexy on fertility

Indication	Study design	Study quality	Consistency	Directness (population, interventions and outcomes reflect study question)	Overall rating*
Effects of orchidopexy on fertility	1 systematic review 9 observational studies	The studies generally compared the effect on fertility of performing orchidopexy in different age groups. The study patients were stratified according to age at orchidopexy. Patient characteristics other than age was generally not provided, therefore it is difficult to ascertain if the differences in results could have been associated with patient characteristics (other than age). Outcomes evaluated included paternity, or surrogate outcomes (hormone levels, testicular volume, cell counts, and sperm motility among others).	There seems to be a trend to a higher number of cells if orchidopexy is performed before the age of 2-3 years compared to older ages, especially in unilateral cryptorchidism. However, the association of surrogate outcomes with clinical outcomes does not seem to be proven. The clinical significance of the magnitude of differences between the study groups was not discussed by the authors.	It needs to be taken into consideration if the outcomes used in the study were appropriate with regards to clinical significance.	**Level of evidence** 2 minus (**Strength of recommendations** Not applicable¦

*Overall rating according to the GRADE working group[5,6]

Table 65 Evidence table, effects of orchidopexy on malignancy

Indication	Study design	Study quality	Consistency	Directness (population, interventions and outcomes reflect study question)	Overall rating*
Effects of orchidopexy on malignancy	2 meta-analyses 1 systematic review 3 cohort/case-control studies	The meta-analyses pool data from different observational studies that may have included patients with different characteristics, or different methods of outcome measurement or adjustment for confounders.	Results in general suggest that undergoing surgery at an older age increases the risk of testicular cancer.	The outcome is relevant. The age cut-off was > 10 years in most studies, which is higher than the age in which patients undergo orchidopexy currently. Observational studies include subgroups with younger age, 0-6 years, however, the number of patients, and especially the number of cases in this subgroup is smaller leading to imprecision in study results. Additionally, patients with diagnoses other than congenital cryptorchidism (acquired cryptorchidism, retractile testes) may have been included in the studies which may affect the results.	**Level of evidence** 1+ (however it could be downgraded if the issues with age and inclusion of patients with diagnoses other than congenital cryptorchidism are deemed to greatly affect the outcomes and generalizability of results to the population of interest **Strength of recommendations** B (see comments above)

*Overall rating according to the GRADE working group[5,6]

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