Pediatr Surg Int (2014) 30:87–97
DOI 10.1007/s00383-013-3429-y

ORIGINAL ARTICLE

Ideal timing of orchiopexy: a systematic review

Emily Chan · Carolyn Wayne · Ahmed Nasr · FRCSC for the Canadian Association of Pediatric Surgeon Evidence-Based Resource

Accepted: 1 November 2013 / Published online: 15 November 2013

Abstract The ideal management of cryptorchidism is a highly debated topic within the field of pediatric surgery. The optimal timing of orchiopexy is particularly unclear, as existing literature reports mixed recommendations. The aim of this study was to determine, based on a systematic review, the most favorable age at which orchiopexy should be performed. We conducted a systematic search of MEDLINE, Embase, CINAHL, and the Cochrane Library to find relevant articles. Two researchers quality assessed each study using the following tools: AMSTAR (systematic reviews), Jadad (RCTs), and MINORS (non-RCTs). We developed a conclusion based on the highest quality studies. We found one relevant systematic review, one RCT, and 30 non-RCTs. Fertility potential was greatest when orchiopexy was performed before 1 year of age. Additionally, orchiopexy before 10–11 years may protect against the increased risk of testicular cancer associated with cryptorchidism. Orchiopexy should not be performed before 6 months of age, as testes may descend spontaneously during the first few months of life. The highest quality evidence recommends orchiopexy between 6 and 12 months of age. Surgery during this timeframe may optimize fertility potential and protect against testicular malignancy in children with cryptorchidism.

Keywords Cryptorchidism · Orchiopexy · Fertility · Testicular cancer · Systematic review

E. Chan · C. Wayne · A. Nasr (✉)
Department of Pediatric Surgery, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON K1H 8L6, Canada
e-mail: anasr@cheo.on.ca

Introduction

Cryptorchidism, the failure of one or both testes to descend into the scrotum prenatally, occurs in 2.4–5 % of newborns [1, 2]. Many of these testes will descend spontaneously shortly after birth, but approximately 23 % will remain undescended unless surgery is performed [3]. If uncorrected, cryptorchidism can affect both fertility and risk for testicular malignancy.

One of the greatest concerns regarding cryptorchidism is the potential for impaired fertility. The most direct measure of male fertility is time until conception of a live born child [4]; however, due to the difficulty in assessing this outcome among formerly cryptorchid patients, previous research has employed various other measures to estimate fertility. These include testicular volume and/or growth, testicular histology at orchiopexy (e.g., germ cells per tubule, tubular diameter, presence of Leydig cells), and semen analysis in adulthood (e.g., sperm concentration, sperm cell count) [5]. Many of these measures have been correlated with paternity rates and time to conception [6–8], and thus have been routinely used as estimates of fertility potential. By employing these measures, researchers have shown that fertility may be impaired as early as 1–2 years of age in cryptorchid boys [9].

Individuals with cryptorchidism are also at increased risk for testicular cancer. The exact mechanism linking cryptorchidism to testicular malignancy is unknown, although several risk factors have been proposed, including testicular atrophy and the increased temperature of the inguinal or abdominal region where the cryptorchid testis is located [9, 10].

It is well known that with early correction of cryptorchidism, the risk of infertility and testicular cancer can be greatly reduced [11, 12]. Over the past few decades, the

recommended age of corrective surgery (orchiopexy) has decreased from 10 years of age in the 1950s and 1960s, to 1–2 years of age in the 1990s and 2000s [13]; however, the optimal age for this procedure is still widely debated. While surgeons are aware of the risks associated with late correction of cryptorchidism, they may be reluctant to operate on a very young infant due to the technical difficulty and operative risk. They are also mindful of the fact that the testis may spontaneously descend with time, and may hesitate to put a young child through a potentially unnecessary procedure.

Unfortunately, there is a scarcity of long-term, prospective studies investigating this topic, and the existing evidence is vague and conflicting. Some studies report optimal fertility outcomes when orchiopexy is performed within the first year [14, 15], while others report satisfactory findings as long as orchiopexy is performed before 2 years of age [16, 17]. Without clear indication of which studies are most valid, clinicians remain in disagreement about the ideal timing of this procedure. To address this problem, we conducted a systematic evaluation of orchiopexy research, focusing on fertility and testicular malignancy outcomes, and assessing the quality of each study. From there, we were able to reach a conclusion regarding the ideal timing of orchiopexy in cryptorchid children, based on the highest quality research available.

To our knowledge, this is the first systematic review to assess the ideal timing for orchiopexy with respect to both fertility and malignancy outcomes. This research was carried out as part of the development of the Canadian Association of Pediatric Surgeons (CAPS) Evidence-Based Resource [18]. This web-based resource has been created to address the lack of evidence-based practice in pediatric surgery, which is caused in part by the paucity of good quality evidence in this area. The authors of the resource use a Delphi-like method [19] to identify the most controversial topics in pediatric surgery, gather and assess the existing evidence for each topic, and present the recommendations from the highest quality research on the website. By making the relevant evidence easily accessible to medical professionals, this resource will promote the implementation of evidence-based surgery in pediatric practice.

Methods

Identification of study topic

We used a Delphi-like method [19] to determine the issues of greatest concern to pediatric surgeons regarding the surgical management of cryptorchid testes. We identified experts with proficiency in this area, based on the number of previous publications.

First round

We sent an online survey to 34 experts. This survey was hosted on the CAPS website and consisted of the open-ended question: "In your practice with the surgical management of cryptorchidism, what issues do you find to be controversial and in need of further research and/or consensus?"

Second round

Based on the results of the first round, we developed a questionnaire listing all the issues raised by the experts. We sent this questionnaire to the responders from the first round, asking them to indicate the three issues that they felt were the most important. The issue that received the most votes was the topic of this study.

Literature search

We conducted electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 onwards), Embase (1980 onwards), and CINAHL (1982 onwards) to find relevant articles. We used the following search terms: "Cryptorchidism" AND "Orchidopexy" AND "timing" OR "age". We included only English publications and studies pertaining to humans and males. We also excluded any editorials and case reviews. We hand-searched the reference sections of relevant articles for additional studies.

Study selection

We included all studies that examined the effect of age at orchiopexy on fertility or malignancy, even if these outcomes were not the primary focus. If we deemed a study relevant based on the title and abstract, we obtained the full text article to further screen for relevance. Two researchers independently performed each level of screening, comparing the selected studies to reach a consensus. If a consensus could not be reached, they consulted a third researcher.

Quality assessment

Systematic reviews and meta-analyses

We used the AMSTAR [20] tool to assess the quality of all relevant systematic reviews. This tool contains 11 items, for a maximum score of 11. Higher scores are indicative of greater methodological quality. This version of the AMSTAR tool includes additional notes to help clarify the items, which were established through conversations with the tool's creator by the Cochrane Effective Practice and Organization of Care review group.

Randomized controlled trials (RCTs)

We used the Jadad et al. [21] tool to assess the quality of all relevant RCTs. This scale contains seven items, two of which are reverse-scored. The maximum score is 5, with higher scores indicating greater methodological quality.

Non-randomized studies (non-RCTs)

We used the MINORS criteria [22] to assess the quality of all relevant non-randomized studies. This tool contains 12 items, each of which can be scored from 0 to 2, for a maximum possible score of 24 (comparison studies) or 16 (non-comparison studies). Higher scores are indicative of greater methodological quality.

Two researchers independently assessed each study, comparing the scores for each item on each tool to reach a consensus. If no consensus could be reached, they consulted a third researcher.

Data extraction and summarization

One researcher extracted data from each of the included studies, and a second researcher checked the data for accuracy and completeness. Based on the studies with the highest methodological quality, we formed a conclusion regarding the optimal timing of orchiopexy to preserve fertility and prevent malignancy.

We present the results based on their outcome of interest, divided by level of evidence. We consider systematic reviews and meta-analyses to be the highest quality evidence, followed by RCTs, non-randomized comparison studies, and non-randomized non-comparison studies.

Results

Literature search and screening

Our initial search yielded 198 studies. After screening, we quality assessed the 32 remaining studies that met our criteria (Fig. 1). Publication dates ranged from 1974 to 2011. Due to the heterogeneity of the data, we could not conduct a meta-analysis.

Outcome 1: fertility

Systematic reviews and meta-analyses

We did not find any systematic reviews or meta-analyses reporting on the impact of age at orchiopexy on fertility (Table 1).

Randomized controlled trials

We found one RCT that included fertility potential as an outcome [14] which received a Jadad score of 3. The authors of this study randomized cryptorchid infants to receive orchiopexy at either 9 months ($n = 72$) or 3 years ($n = 83$). Fertility potential was defined as testicular catch-up growth between 9 months and 4 years of age. Boys who underwent orchiopexy at 9 months of age had significant catch-up growth of the repaired testis, while those who underwent orchiopexy at 3 years had no testicular growth before or after surgery.

Non-randomized studies

We found 23 comparative non-RCTs [11, 15–17, 23–41], with MINORS scores ranging from 11 to 20, and 4 non-comparative studies, with MINORS scores from 6 to 12. Due to the low quality of the non-comparative studies, we have chosen to report primarily on the findings of the comparative non-RCTs.

Altogether, the comparative studies included 3,099 patients with a history of cryptorchidism. There were five studies that estimated fertility potential based on testicular volume or testicular growth [16, 28, 31, 33, 34]. Consistent with the RCT [14], the overall consensus was that earlier orchiopexy resulted in greater testicular growth and/or volume, although the youngest age group among these studies was <18 months at orchiopexy.

Several studies reported on testicular histology at the time of orchiopexy [15, 23, 26, 27, 32, 36, 41]. Various outcomes were examined to determine fertility potential (e.g., seminiferous tubule diameter, germ cells per tubule; Table 1). The highest quality studies showed that fertility potential was greatest when orchiopexy was performed before 1 year of age. For example, Park et al. [15] reported that germ cell count and mean tubular fertilization rate (percentage of tubules containing at least one germ cell) were significantly higher in cryptorchid infants <1 year of age compared with other age groups. Similarly, when comparing patients <1 year, 1–2 years, 2–3 years, and 3–4 years of age, Kogan et al. [23] found that seminiferous tubule diameter decreased significantly with each subsequent age group. In addition, Tasian et al. [26] showed that the odds of germ cell depletion doubled when orchiopexy was performed at 2 years compared with 1 year of age.

Some studies also reported on semen analysis in adulthood (i.e., sperm count, sperm concentration) [11, 25, 29–32, 35, 37, 38, 40, 41]. The overall consensus was that earlier orchiopexy had better outcomes; specifically, the highest quality study [11] showed that sperm count and highly motile spermatozoa were significantly increased when orchiopexy was performed at <1 year compared to 1–2 years of age.

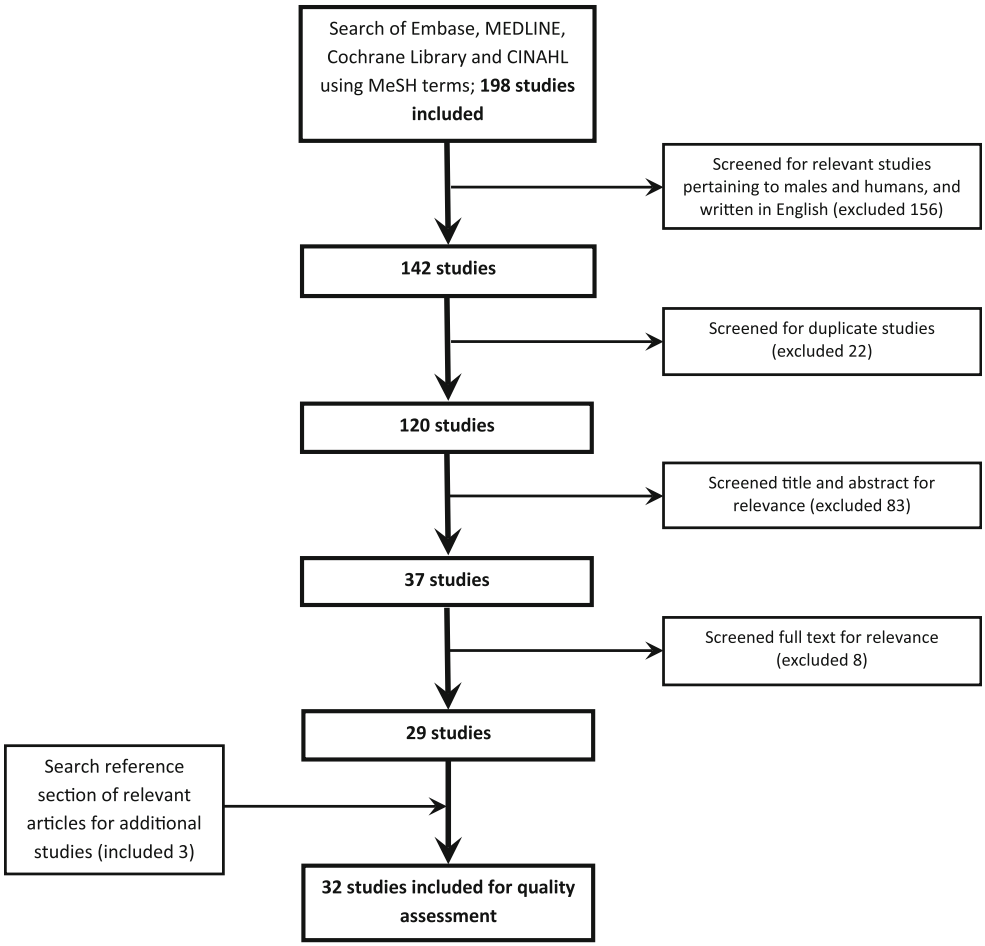

Fig. 1 Electronic search methodology and study selection

There was only one comparative non-RCT that attempted to measure paternity after orchiopexy [24]. The authors found no difference in paternity rates between patients who had undergone orchiopexy at <7 years and those who had orchiopexy at ≥7 years of age.

Outcome 2: testicular malignancy

Systematic reviews and meta-analyses

We found one systematic review and meta-analysis for this outcome [42], which had a score of 4 on the AMSTAR scale. This study included five observational studies (two cohort studies and three case–control studies) and dichotomized patients into two age groups (orchiopexy before or after age 10–11). All included studies assessed both the association of cryptorchidism with testicular cancer and the risk of cancer by age at orchiopexy. This systematic review indicated that men with a history of cryptorchidism were 1.6–7.5 times more likely to develop testicular cancer, compared with the general population. In addition, patients who underwent orchiopexy after 10–11 years were 2.9–32.0 times more likely to develop testicular cancer than those who underwent earlier correction. Similarly, their meta-analysis indicated that boys in the older group at orchiopexy were three times more likely to develop cancer than those in the younger group, although this difference was not statistically significant. Nevertheless, the authors concluded that orchiopexy before age 10–11 may lessen the increased risk of testicular cancer associated with cryptorchidism (Table 2).

Randomized controlled trials

We did not find any RCTs that included malignancy as an outcome.

Non-randomized studies

We found seven non-RCTs [12, 43–48], all of which were comparative, with MINORS scores ranging from 14 to 19. There were three cohort studies, which included 21,026 patients with a history of cryptorchidism. The remaining four studies (prospective and retrospective) comprised

Table 1 Studies assessing impact of age at orchiopexy on fertility

Study	Study period	Study design	*N*	Laterality	Measure of fertility	Comparison groups (age at surgery)	Findings	Score
RCT								Jadad
Kollin et al. [14]	1998–2005	Randomized, controlled	155	Unilateral	Testicular growth	9 months, 3 years	Orchidopexy at 9 months resulted in significant catch-up growth of the undescended testis up until 4 years of age, while orchidopexy at 3 years showed no significant growth of the undescended testis before or after surgery	3
Non-RCT								MINORS
Park et al. [15]	1998–2001	Prospective	65	Unilateral	Tubular diameter, germ cells per tubule (GCC), tubular fertilization rate (MTFR), Sertoli cell index (SCI), interstitial fibrosis index (IFI)	<1 year, 1–2 years, 2–4 years, >4 years	GCC and MTFR were significantly higher in <1 year compared with all other groups. IFI was significantly higher in >4 years, compared with all other groups	20
Kogan et al. [23]	Not given	Retrospective	77	Unilateral	Tubular diameter, germ cells per tubule	2–11 months, 12–23 months, 24–35 months, 36–46 months	Each subsequent age group had a significant decrease in tubular diameter, except the oldest group. Germ cell count did not differ among the groups.	18
Lee et al. [24]	1955–1971	Retrospective with follow-up[a]	421 + 470 controls	Unilateral	Paternity	<7 years, ≥7 years	No difference in paternity between the two groups	18
Canavese et al. [11]	1986–1991	Retrospective with follow-up	29	Unilateral and bilateral	Total sperm count, sperm motility, testicular volume, presence of Ad spermatogonia	<1 year, 1–2 years	Significantly higher sperm count and greater proportion of highly motile spermatozoa in those <1 year	17
Kim et al. [16]	2007–2008	Retrospective with follow-up	108	Unilateral	Testicular volume	<2 years, 2–5 years, >5 years	Significantly greater testicular growth in those <2 years, compared with the other groups	17
Wiser et al. [25]	1996–2004	Retrospective with follow-up	42	Unilateral and bilateral	Successful testicular sperm extraction, levels of FSH, LH, testosterone	≤10 years, >10 years	No differences between groups for any outcomes	17
Tasian et al. [26]	1991–2001	Retrospective	274	Unilateral and bilateral	Degree of peritubular fibrosis, germ cells per tubule, presence of Leydig cells	0–12 months, 13–24 months, 25–96 months, >96 months	Odds of germ cell depletion doubled for each subsequent age group. Age was a significant predictor of germ cell depletion and Leydig cell loss	16
McAleer et al. [27]	1986–1990	Retrospective	226	Unilateral and bilateral	Spermatogonia per tubule	<1 year, 1–1.5 years, 1.5–2 years, >2–6 years	After the first year of life, spermatogonia decreased significantly from age-expected values	15
Mengel et al. [17]	1962–1972	Retrospective	447	Unilateral and bilateral	Integrity of germinal epithelium of testes, spermatogonia count, tubular diameter	<2 years, >2 years	No visible damage to testes <2 years of age, spermatogonia count and tubular diameter significantly decreased below normal for >2 years, but not for <2 years	15

Table 1 continued

Study	Study period	Study design	*N*	Laterality	Measure of fertility	Comparison groups (age at surgery)	Findings	Score
Taskinen et al. [28]	1966–1977	Retrospective with follow-up	75	Unilateral and bilateral	Testicular volume	0–2 years, 3–5 years, 6–13 years	No significant difference among the groups	15
Cortes et al. [41]	1971–2000	Retrospective with follow-up	140	Unilateral and bilateral	Spermatogonia and gonocytes per tubule at orchiopexy; sperm count, FSH, LH and testosterone at follow-up	0–3 years, 4–7 years, 8–11 years	Increased frequency of germ cell loss as age at surgery increased; in bilateral cryptorchids only, lower germ cell count was correlated with lower sperm concentration in adulthood	14
Engeler et al. [31]	1970–1979	Retrospective with follow-up	35	Bilateral	Testicular volume, sperm concentration	<2 years, ≥2 years	Testicular volume was significantly greater in patients who underwent surgery before 2 years; age at surgery was inversely correlated with both sperm concentration and total testicular volume	14
Taskinen et al. [40]	1966–1977	Retrospective with follow-up	51	Unilateral and bilateral	Semen quality (sperm concentration, motility, morphology)	<4 years, ≥4 years	Unilateral: no difference in sperm concentration between groups. Bilateral: significantly greater sperm concentration in patients treated at <4 years	14
Trsinar et al. [29]	1974–1985	Retrospective with follow-up	68	Unilateral and bilateral	Sperm concentration, motility and morphology; levels of FSH and inhibin B	<8 years, ≥8 years	No differences in sperm concentration and motility between groups; patients who had surgery at <8 years had significantly higher inhibin B and testicular volume, and lower FSH	14
Coughlin et al. [30]	1955–1974	Retrospective with follow-up	84	Unilateral	FSH, LH, testosterone, inhibin B, sperm density	<2 years, ≥2 years	Age at surgery was negatively correlated to inhibin B and sperm density, and positively correlated to FSH; patients who had surgery at <2 years had significantly higher inhibin B and lower FSH	13
Hadziselimovic et al. [32]	Not given	Retrospective with follow-up	31	Unilateral and Bilateral	Germ cell count at orchiopexy, sperm cell count at follow-up	<6 months, 6 months–2 years	Germ cell count was highest when orchiopexy was before 6 months; no difference in sperm cell count among groups.	13
Nagar et al. [33]	1990–1995	Retrospective	190	Unilateral	Testicular growth	<18 months, ≥18 months	Testicular growth most common in patients who had surgery at <18 months	13
Riebel et al. [34]	1986–1996	Retrospective with follow-up	68	Unilateral and bilateral	Testicular morphology	<3 years, 3–8 years	No difference in morphology between groups	12
Lee et al. [35]	1955–1974	Retrospective with follow-up	106 + 52 controls	Unilateral	Testicular volume, sperm density, FSH, LH, inhibin B, testosterone	No comparison between age groups	In patients, testosterone correlated negatively with age and positively with inhibin B, sperm density, and normal sperm motility and morphology	11

Table 1 continued

Study	Study period	Study design	*N*	Laterality	Measure of fertility	Comparison groups (age at surgery)	Findings	Score
Lala et al. [36]	Not given	Prospective	56	Unilateral and bilateral	Epididymal morphology, tubular histology, appearance of peritubular connective tissue, Leydig cell morphology, fibrosis of interstitial space	No comparison	Negative correlation between germ cell count and age at surgery; positive correlation between tubular atrophy and age	12
Gracia et al. [37]	Not given	Retrospective with follow-up	251	Unilateral and bilateral	FSH, LH, testosterone, sperm density	No comparison	No correlation between sperm density and age at surgery; FSH, LH and sperm density significantly higher in unilateral vs bilateral cryptorchids	10
Puri et al. [38]	1957–1975	Retrospective with follow-up	142	Unilateral and bilateral	Semen quality (volume density, motility, morphology)	No comparison	When orchiopexy is performed between 7–13 years, 74 % of unilateral cryptorchids compared with 30 % of bilateral cryptorchids	9
Kumar et al. [39]	1950–1975	Retrospective with follow-up	113	Unilateral and bilateral	Average age at first paternity	No comparison	Orchiopexy after age 18 seems to be associated with higher age at first paternity	6

[a] Retrospective with follow-up: authors identified patients retrospectively but recruited them prospectively

1,661 cases. Most of these studies were already included in the systematic review by Walsh [42, 43, 45–48], thus it was not surprising that the conclusion of the highest quality studies was the same as that of Walsh: risk of testicular cancer increased with delayed surgery, especially after 10 years of age. However, these studies had mixed conclusions regarding the relative risk of testicular cancer compared with non-cryptorchid controls. Some studies reported an increased risk of cancer even when orchiopexy was performed before puberty [12, 43], while others found no increased risk of cancer for these patients [44, 45, 47]. The highest quality study [43] reported a relative risk of 2.6 for patients who had undergone orchiopexy before 10 years.

Discussion

The ideal timing of orchiopexy for cryptorchidism has long been debated. Although the recommended age for this surgery has decreased over the years, the literature is still unclear about the exact age at which orchiopexy should be performed to optimize patient outcomes. In this systematic review, we assessed the quality of all studies pertaining to this topic and developed recommendations based on the highest quality evidence. Previous research has focused on two main outcomes after cryptorchidism: fertility and testicular malignancy. Regarding fertility, several measures have been examined, including testicular growth/size, testicular histology, semen analysis, and paternity rate. Most of these measures serve as surrogates of fertility, as paternity rate and time until conception are the only direct measures of male fertility. For the single study that reported on paternity rate after cryptorchidism [24], we were cautious about interpreting their results; this study compared patients <7 years and ≥7 years at orchiopexy, however, research has consistently shown that fertility potential may be impaired as early as the first year of life [11, 14, 15, 23, 26, 27, 32]. The overall conclusion from the highest quality studies reporting on fertility potential after cryptorchidism was that orchiopexy should be performed before 1 year of age to optimize fertility outcomes. However, spontaneous descent of the testes can occur until approximately 6 months of age. Wenzler et al. [49] found that cryptorchid infants aged 6 months or older did not achieve spontaneous descent, while 13 % of those who presented before 6 months achieved spontaneous descent by 1 year of age. Similarly, other studies have observed spontaneous descent within the first few months of life in full-term infants, but very rarely after 6 months of age [50, 51]. Thus, we recommend that orchiopexy be performed after 6 months of age, to allow for possible natural descent. If the testis remains cryptorchid after 6 months,

Table 2 Studies assessing impact of age at orchiopexy on testicular malignancy

Study	Study period	Study design	*N*	Age at surgery	Risk of malignancy	Score
Systematic review						AMSTAR
Walsh et al. [42]	1951–1996	Systematic review and meta-analysis	5 studies	<10–11 years, >10–11 years	Patients with surgery after 10–11 were 2.9–32.0 times more likely to develop testicular cancer; meta-analysis: surgery after 10–11 3 times more likely to develop cancer	4
Non-RCT						MINORS
Strader et al. [43]	1977–1983	Prospective	333 + 675 controls	<10 years, ≥10 years	Patients with a history of cryptorchidism were 5.9 times more likely to develop cancer, but those with orchiopexy before 10 years had a smaller increase in risk	19
Forman et al. [44]	1984–1987	Retrospective with follow-up	794	<10 years, ≥10 years	Patients with orchiopexy ≥10 years have a risk estimate of 3.82	17
Herrinton et al. [45]	1973–1996	Retrospective	20	<11 years, ≥11 years	Patients with orchiopexy ≥11 years were 32 times more likely to develop cancer	17
Møller et al. [46]	1986–1988	Prospective	514 + 720 controls	<10 years, 10–14 years, ≥15 years	Increased risk of testicular cancer with each subsequent age group	15
Pettersson et al. [12]	1964–1999	Retrospective cohort	16,983	<13 years, ≥13 years	Relative risk if treated <13 years: 2.23, if treated ≥13 years: 5.40	15
Pinczowski et al. [47]	1965–1984	Retrospective cohort	2,919	0–4 years, 5–9 years, 10–14 years, ≥15 years	Relative risk if treated 0–9 years: 0, if treated 10–14 years: 3.9, if treated ≥15 years: 20.3	15
Swerdlow et al. [48]	1951–1994	Retrospective with follow-up, cohort	1,124	0–4 years, 5–9 years, 10–18 years	No increased risk	14

orchiopexy should be performed as soon as possible—and certainly before 1 year of age—to optimize fertility outcomes. This conclusion is consistent with the recommendation by a group of experts from five Nordic countries, who suggested that orchiopexy be performed between 6 and 12 months of age [52].

For the second outcome, testicular malignancy, our results indicated that risk for cancer is greatly increased when orchiopexy is delayed until after 10–11 years in cryptorchid boys. There was conflicting evidence regarding whether orchiopexy before this age could eliminate the increased risk of testicular cancer associated with cryptorchidism; however, the highest quality non-RCT [43] indicated that even patients with early orchiopexy (before 10 years) were 2.6 times more likely than non-cryptorchid controls to develop testicular cancer. Thus, to protect against the increased risk of testicular cancer, we recommend that orchiopexy should be performed as early as possible (ideally between 6 and 12 months of age, as this would also optimize fertility potential).

Unfortunately, surgeons do not always correct cryptorchidism at such a young age. Researchers in Austria [53] and New Zealand [13] recently reported that the mean age for orchiopexy was 3.4 years and 4.5 years, respectively. Additionally, a North American study conducted in 2010 found that only 18 % of orchiopexies were performed during the first year of life [54]. There are a few possible reasons for this late correction age. Firstly, primary care providers may not be aware of the optimal age for orchiopexy and may not refer the patient to a specialist during the first year of life. In a survey of pediatricians and general practitioners, only 24 % recommended surgery between 6 and 12 months of age, and 10–30 % recommended orchiopexy between 3 and 10 years of age [55]. Even if a timely referral is made, the delay between the referral and the actual surgery may be quite lengthy. Some researchers have also suggested that cryptorchid testes in older children may be a result of acquired, rather than congenital, undescended testes, possibly caused by cremaster muscle spasm and a patent processus vaginalis [53]. These testes could have been in the scrotum at birth but ascended during childhood, accounting for some of the orchiopexies performed on older children. Finally, some surgeons may be reluctant to operate on very young

patients, as orchiopexy in a small infant is technically challenging and is associated with more failures than when orchiopexy is performed at an older age [56]. For this reason, experts in several Nordic countries have recommended that orchiopexy for infants aged 6–12 months should be performed by pediatric surgeons or pediatric urologists [52]. In addition, other technically challenging orchiopexies (e.g., for bilateral cryptorchidism, non-palpable testes, or re-do surgeries) should be performed by these specialists, regardless of the patient's age. These guidelines may help reduce the number of failures and post-operative complications for difficult orchiopexies.

Our results should be interpreted with caution due to limitations of our study. The most direct measurement of male fertility is paternity rate and time until conception of a live born child [4]; however, due to the difficulty in conducting long-term paternity studies, most research has measured fertility using testicular growth/size [11, 14, 16, 28, 31, 33–35], testicular histology at orchiopexy [15, 17, 23, 26, 27, 32, 36, 41], and semen analysis in adulthood [11, 25, 29–32, 35, 37, 38, 40, 41]. While these outcomes have been correlated with testicular function and paternity rate [6–8, 57, 58], they are not direct measures of fertility, and thus can only be taken as estimates of fertility potential. Furthermore, even though paternity is the most direct measure of fertility, it is difficult to obtain accurate, unbiased results in paternity studies [5]. However, until prospective, long-term studies are conducted, this is the best available evidence.

We were also unable to stratify our results based on testicular location (i.e., inguinal or intra-abdominal), as most of the included studies did not examine outcomes based on the position of the cryptorchid testis. Previous research has shown that testicular location may affect both fertility and malignancy; compared with inguinal undescended testes, intra-abdominal testes were associated with decreased fertility potential [5, 38, 59] and increased malignancy risk [60, 61]. In our review, based on the studies that reported testicular location [11, 14–16, 26, 27, 31, 33, 34, 36, 37], 84–100 % of testes were located either in the inguinal or pre-scrotal location. Thus, our results pertain primarily to such cases.

Furthermore, most of the studies included in our review were non-randomized and observational in nature. As with all non-RCTs, there are many potential sources of bias. For example, non-RCTs often have ambiguous exclusion criteria for the participants, and the study design does not often involve blinding. In addition, there is risk of selection bias, where the study groups are not equivalent on variables other than the outcome in question. To minimize the risk of bias in our study, we have evaluated each non-RCT using the MINORS assessment tool. This scale contains items that address various potential sources of bias. As higher scores are indicative of greater methodological quality and lower risk of bias, we have based our results on only the highest-rated studies.

For this systematic review, we ran a comprehensive search of four major databases and did not set a date limitation; thus, the studies we found should be representative of the available literature. However, we did restrict our search to English language studies only, potentially excluding good quality studies in other languages. Finally, as with all systematic reviews, there is risk of publication bias; many studies without significant results may have gone unpublished, and as such we would not have been able to incorporate them into our review.

In this review, we found that orchiopexy between 6 and 12 months of age may optimize fertility potential and help protect against the increased risk of testicular cancer associated with cryptorchidism. Surgery should not be performed before 6 months, as the testis may descend spontaneously during that time. Furthermore, orchiopexy in infants should be performed by pediatric urologists or pediatric surgeons to reduce the risk of complications. There is a paucity of higher-quality studies (e.g., long-term, prospective randomized trials) investigating the effect of age at orchiopexy on fertility and malignancy, possibly because of ethical concerns with randomization and the feasibility of long-term follow-up. Future research should address these issues, focusing especially on the effect of age at treatment on direct measures of fertility (i.e., time until conception of a live born child), for which existing research is particularly scarce. Nevertheless, our study is the first step towards determining the ideal management of undescended testes. By disseminating our findings, we hope to bring awareness of this topic to pediatric surgeons and other medical practitioners, promoting the worldwide use of evidence-based medicine.

References

1. Cortes D, Kjellberg EM, Breddam M et al (2008) The true incidence of cryptorchidism in Denmark. J Urol 179:314–318
2. Thonneau PF, Candia P, Mieusset R (2003) Cryptorchidism: incidence, risk factors, and potential role of environment; an update. J Androl 24:155
3. Thong M, Lim C, Fatimah H (1997) Undescended testes: incidence in 1,002 consecutive male infants and outcome at 1 year of age. Pediatr Surg Int 13:37–41
4. Pasqualotto FF, Locambo CV, Athayde KS et al (2003) Measuring male infertility: epidemiological aspects. Rev Hosp Clín Fac Med Univ São Paulo 58:173–178
5. Murphy F, Paran TS, Puri P (2007) Orchidopexy and its impact on fertility. Pediatr Surg Int 23:625–632
6. Cendron M, Keating MA, Huff DS et al (1989) Cryptorchidism, orchiopexy and infertility: a critical long-term retrospective analysis. J Urol 142:559–562 discussion 572

7. Bostofte E, Serup J, Rebbe H (1982) Relation between sperm count and semen volume, and pregnancies obtained during a twenty-year follow-up period. Int J Androl 5:267–275
8. Bonde JPE, Ernst E, Jensen TK et al (1998) Relation between semen quality and fertility: a population-based study of 430 first-pregnancy planners. The Lancet 352:1172–1177
9. Comploj E, Pycha A (2012) Diagnosis and management of cryptorchidism. Eur Urol Suppl 11:2–9
10. Batata M, Whitmore W Jr, Hilaris B et al (1976) Cancer of the undescended or maldescended testis. Am J Roentgenol 126:302–312
11. Canavese F, Mussa A, Manenti M et al (2009) Sperm count of young men surgically treated for cryptorchidism in the first and second year of life: fertility is better in children treated at a younger age. Eur J Pediatr Surg 19:388–391
12. Pettersson A, Richiardi L, Nordenskjold A et al (2007) Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med 356:1835–1841
13. Bruijnen CJ, Vogels HD, Beasley SW (2008) Review of the extent to which orchidopexy is performed at the optimal age: implications for health services. ANZ J Surg 78:1006–1009
14. Kollin C, Karpe B, Hesser U et al (2007) Surgical treatment of unilaterally undescended testes: testicular growth after randomization to orchiopexy at age 9 months or 3 years. J Urol 178:1589–1593
15. Park KH, Lee JH, Han JJ et al (2007) Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis. Int J Urol 14:616–621
16. Kim S, Hwang EC, Hwang IS et al (2011) Testicular catch up growth: the impact of orchiopexy age. Urology 78:886–889
17. Mengel W, Hienz H, Sippe W II et al (1974) Studies on cryptorchidism: a comparison of histological findings in the germinative epithelium before and after the second year of life. J Pediatr Surg 9:445–450
18. Canadian association of pediatric surgeons: CAPS evidence-based resource (2013)
19. Graham B, Regehr G, Wright JG (2003) Delphi as a method to establish consensus for diagnostic criteria. J Clin Epidemiol 56:1150–1156
20. Shea BJ, Grimshaw JM, Wells GA et al (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 7:10
21. Jadad AR, Moore RA, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12
22. Slim K, Nini E, Forestier D et al (2003) Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. ANZ J Surg 73:712–716
23. Kogan SJ, Tennenbaum S, Gill B et al (1990) Efficacy of orchiopexy by patient age 1 year for cryptorchidism. J Urol 144:508–509 discussion 512–513
24. Lee PA, O'Leary LA, Songer NJ et al (1996) Paternity after unilateral cryptorchidism: a controlled study. Pediatrics 98:676–679
25. Wiser A, Raviv G, Weissenberg R et al (2009) Does age at orchidopexy impact on the results of testicular sperm extraction? Reprod Biomed Online 19:778–783
26. Tasian GE, Hittelman AB, Kim GE et al (2009) Age at orchiopexy and testis palpability predict germ and Leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. J Urol 182:704–709
27. McAleer IM, Packer MG, Kaplan GW et al (1995) Fertility index analysis in cryptorchidism. J Urol 153:1255–1258
28. Taskinen S, Wikstrom S (1997) Effect of age at operation, location of testis and preoperative hormonal treatment on testicular growth after cryptorchidism. J Urol 158:471–473
29. Trsinar B, Muravec UR (2009) Fertility potential after unilateral and bilateral orchidopexy for cryptorchidism. World J Urol 27:513–519
30. Coughlin MT, Bellinger MF, Lee PA (1999) Age at unilateral orchiopexy: effect on hormone levels and sperm count in adulthood. J Urol 162:986–988
31. Engeler DS, Hösli PO, John H et al (2000) Early orchiopexy: prepubertal intratubular germ cell neoplasia and fertility outcome. Urology 56:144
32. Hadziselimovic F, Herzog B (2001) The importance of both an early orchidopexy and germ cell maturation for fertility. The Lancet 358:1156–1157
33. Nagar H, Haddad R (1997) Impact of early orchidopexy on testicular growth. Br J Urol 80:334–335
34. Riebel T, Herrmann C, Wit J et al (2000) Ultrasonographic late results after surgically treated cryptorchidism. Pediatr Radiol 30:151–155
35. Lee PA, Coughlin MT (2002) Leydig cell function after cryptorchidism: evidence of the beneficial result of early surgery. J Urol 167:1824–1827
36. Lala R, De Sanctis C, Canavese F et al (1992) Early medical and surgical treatment of cryptorchidism: clinical, anatomic, and histologic findings. Pediatr Surg Int 7:368–371
37. Gracia J, Sanchez Zalabardo J, Sanchez Garcia J et al (2000) Clinical, physical, sperm and hormonal data in 251 adults operated on for cryptorchidism in childhood. BJU Int 85:1100–1103
38. Puri P, O'Donnell B (1988) Semen analysis of patients who had orchidopexy at or after seven years of age. Lancet 332:1051–1052
39. Kumar D, Bremner D, Brown P (1989) Fertility after orchiopexy for cryptorchidism: a new approach to assessment. Br J Urol 64:516–520
40. Taskinen S, Hovatta O, Wikstrom S (1996) Early treatment of cryptorchidism, semen quality and testicular endocrinology. J Urol 156:82–84
41. Cortes D, Thorup M Jr, Visfeldt J (2001) Cryptorchidism: aspects of fertility and neoplasms. Horm Res Paedia 55:21–27
42. Walsh TJ, Dall'Era MA, Croughan MS et al (2007) Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer. Comment J Urol 178:1440–1446
43. Strader CH, Weiss NS, Daling JR et al (1988) Cryptorchism, orchiopexy, and the risk of testicular cancer. Am J Epidemiol 127:1013–1018
44. Forman D, Pike M, Davey G et al (1994) Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise. BMJ 308:1393–1399
45. Herrinton LJ, Zhao W, Husson G (2003) Management of cryptorchism and risk of testicular cancer. Am J Epidemiol 157:602–605
46. Møller H, Prener A, Skakkebxk NE (1996) Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: case-control studies in Denmark. Cancer Causes Control 7:264–274
47. Pinczowski D, McLaughlin J, Läckgren G et al (1991) Occurrence of testicular cancer in patients operated on for cryptorchidism and inguinal hernia. J Urol 146:1291
48. Swerdlow A, Higgins C, Pike M (1997) Risk of testicular cancer in cohort of boys with cryptorchidism. BMJ 314:1507–1511
49. Wenzler DL, Bloom DA, Park JM (2004) What is the rate of spontaneous testicular descent in infants with cryptorchidism? J Urol 171:849–851
50. Hamza A, Elrahim M, Elnagar O et al (2001) Testicular descent: when to interfere? Eur J Pediatr Surg 11:173–176
51. Virtanen H, Toppari J (2008) Epidemiology and pathogenesis of cryptorchidism. Hum Reprod Update 14:49–58
52. Ritzén EM, Bergh A, Bjerknes R et al (2007) Nordic consensus on treatment of undescended testes. Acta Paediatr 96:638–643 Oslo, Norway: 1992

53. Springer A, Huber C, Reck C et al (2010) Delayed referral despite appropriate knowledge in cryptorchidism as a cause of delayed orchidopexies in Austria. Klinische Pädiatrie 222:248–251
54. Kokorowski PJ, Routh JC, Graham DA et al (2010) Variations in timing of surgery among boys who underwent orchidopexy for cryptorchidism. Pediatrics 126:576–582
55. Steckler RE, Zaontz MR, Skoog SJ et al (1995) Cryptorchidism, pediatricians, and family practitioners: patterns of practice and referral. J Pediatr 127:948–951
56. Thorup J, Jensen C, Langballe O et al (2011) The challenge of early surgery for cryptorchidism. Scand J Urol Nephrol 45:184–189
57. Bujan L, Mieusset R, Mansat A et al (1989) Testicular size in infertile men: relationship to semen characteristics and hormonal blood levels. Br J Urol 64:632–637
58. Takihara H, Cosentino M, Sakatoku J et al (1987) Significance of testicular size measurement in andrology II. Correlation of testicular size with testicular function. J Urol 137:416
59. Puri P, Sparnon A (1990) Relationship of primary site of testis to final testicular size in cryptorchid patients. Br J Urol 66:208–210
60. Wood HM, Elder JS (2009) Cryptorchidism and testicular cancer: separating fact from fiction. J Urol 181:452–461
61. Elder J (1988) The undescended testis. Hormonal and surgical management. Surg Clin North Am 68:983–1005