Peer reviewed article

Management of cryptorchidism in children: guidelines

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Summary

Question: To develop clinical guidelines for the management of cryptorchidism in pre-pubertal boys, from early diagnosis through therapy to long-term follow-up and prognosis.

Method: Systematic review of articles from the medical literature, referenced since 1966, using validated search strategies through the following databases: Medline, Cochrane Database of Systematic Reviews, Cochrane Register of Controlled Trials, EMBASE, DARE, ACP Journal Club, National Guidelines Clearinghouse, Guidelines International Network. Relevant articles published after 1988 were taken as the basis for the statements. Each statement was graded on the basis of the study design and on its methodological quality (GRADE approach). A multidisciplinary panel of local experts discussed and evaluated each statement on the strength of this evidence.

Results: 28 statements based on the best available evidence were drafted. The experts agreed with all but two statements, which were rated uncertain.

Conclusions: Cryptorchidism is best diagnosed clinically, and treated by surgical orchiopexy at age 6–12 months, without a routine biopsy. If no testis is palpable, or if other signs of hypovirilisation such as hypospadias are present, the chromosomal sex and hormonal status must be assessed. Laparoscopy is the best way of diagnosing and managing intra-abdominal testes.

Key words: cryptorchidism; guidelines; evidence-based medicine

Introduction

Cryptorchidism, defined as the absence of at least one testis in the scrotum [1], is a frequent condition in the paediatric population. It affects up to 9% of full-term newborns and up to 1.5% of one-year-old boys [2], and may involve the use of considerable medical and economic resources, arguably to prevent its potential long-term complications: cancer and impaired fertility. Unclear definitions and conflicting results from the medical literature make its management still a much-debated issue [3, 4].

Practice guidelines based on a sound evidence-based methodology are a tool proposed to caregivers and their patients to help them make proper decisions according to the best available scientific evidence [5]. They have no coercive value. They should address an issue with important health implications and wide variability of management and existing scientific data, all of which criteria are fulfilled for cryptorchidism.

Our aim was to obtain clinical practice guidelines on the management of cryptorchidism in pre-pubertal boys, from early diagnosis through therapy to long-term follow-up and prognosis.

No external financial support.

Methods

A systematic review of the literature was conducted using search strategies of English, French, German and Italian published articles referenced in Medline between 1966 and March 2006. The search strategy is detailed in Table 1. Similar searches were conducted in other databases (EMBASE, Cochrane Register of Controlled Trials, DARE, ACP Journal Club). In addition, we searched the Cochrane Database of Systematic Reviews, the National Guidelines Clearinghouse and the Guidelines International Network for systematic reviews and published guidelines to be adapted, if any. Our initial goal was to adapt existing guidelines to a proposed adaptation approach [6]. In the absence of such guidelines we decided to develop them *de novo*. We thus based their development on the systematic literature search described above. Table 1 indicates the search strategy used in Medline (Ovid), which was adapted for the other databases. Table 2 indicates the definitions we adopted. We first ruled out irrelevant articles based on abstract reading. We arbitrarily decided to keep only articles published after 1988, making exceptions for milestone articles that had not been included in more recent updates or reviews. The management of retrieved references was performed with the support of Reference Manager©. Each article was first graded from I to V according to the level of evidence (I: randomised controlled trial or systematic review thereof; II: non-randomised, controlled trial; III: prospective cohort study; IV: retrospective (historical) or case-control study; V: case series or experts' opinion). In addition, we used the GRADE approach to better evaluate the level of evidence and the strength of recommendations, taking the design and the quality of studies into consideration [7]. The expected best type of design varied according to the clinical question, e.g. a randomised controlled study for treatment, a study of the evaluation of a diagnostic test's efficacy or a prospective cohort study to evaluate prognosis. We also rated, but did not report, the quality of randomised controlled trials (RCTs) using Jadad's score [8]. A series of statements was developed on the basis of the articles retrieved. For each of them we reported the quality of evidence and the strength of statements. These guidelines do not address cryptorchidism as part of a syndrome.

A panel of local experts met to discuss and rate these statements, bearing the evidence in mind. The panel tried to reach a consensus, if possible, but consensus was not forced. The experts included 4 paediatric surgeons (PF, BJM, PR, CG), one paediatrician (FC), one paediatric radiologist (FG), one paediatric endocrinologist (GT), one urologist (PJ) and one epidemiologist (BB). Using a modified Delphi technique [9], further adapted to be used for the explicit rating of guideline statements [10], the experts formally rated each statement on a 1–9 scale (1 totally disagree, 9 totally agree). We consolidated these results in three categories (agree, uncertain, disagree) based on the median agreement score and the degree of agreement between the experts. The median score was ascertained for each statement. In the absence of discordance (no more than 2 scores between 1–3 and no more than 2 scores between 7 and 9), the vote was considered to reflect agreement when the median score was more than 7, uncertainty when between 4 and 6, and disagreement when between 1 and 3.

Results and comments

We did not find existing guidelines covering the same issues and thus had to to develop guidelines anew; 399 articles were considered relevant, analysed and graded. The quality of evidence and the strength of the statements are summarised in Table 3. The quality of evidence did depend on the design of the study. Twenty-eight statements were developed. The experts agreed with all but two statements, which were rated uncertain. A more detailed description follows below, in various paragraphs, according to the key topics structuring the answers to the clinical questions about early diagnosis and management of cryptorchidism.

After the end of our review process, Ritzén et al published the Nordic consensus on treatment of undescended testes, along with an update of the literature [11].

Epidemiology

The prevalence of cryptorchidism at birth is 2.5–9%, with marked geographic variations. Prevalence at 3 months is 1–1.9% and 0.8–1.5% at 18 months [12]. Bilateral presentation is found in 10–20% of cases. An oft suggested increase in prevalence in more recent times has not been proven so far [13, 14]. In any event, it appears that more orchidopexies are performed than expected from prevalence data [15]. Risk factors include genetic predisposition, pre-term birth, low birth weight and prenatal exposure to hormonal disruptors or tobacco in either the mother or the father [16–19].

Risk to subsequent fertility

We decided to stress paternity studies against sperm-count values, endocrinological and histological studies, since the latter represent only surrogate endpoints (fertility *potential*). Sperm counts and hormone levels of cryptorchid patients may be altered. However, while abnormal laboratory tests suggest impaired fertility, they scarcely correlate with actual fatherhood in paternity studies and show considerable overlap between cryptorchid patients and the normal population. The lower norm for sperm concentration values set at 20 million/mL by the WHO should be treated with caution, as this parameter alone may not be a reliable indicator of male fertility [1, 20–22].

Patients with untreated bilateral cryptorchidism have a very high risk of sterility (abnormal sperm count in 100%; no paternity studies available). If the condition has been corrected the risk falls to 38% in paternity studies. Age at treatment has not been investigated in these studies. Testis location before treatment has no impact on fertility [23]. Paternity chances in patients with treated unilateral cryptorchidism are almost nor-

Table 1

Search strategy, as used in Medline / Ovid.

CRYPTORCHIDISM
1. Cryptorchidism/
2. empty scrotum.tw
3. undescended test$.tw
4. maldescensus test$.tw
5. non-descended test$.tw
6. ectopic test$.tw
7. retractile test$.tw
8. cryptorchi$.tw
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. limit 9 to human
11. limit 10 to (english or french or german or spanish or italian)
GUIDELINES
12. guideline$.tw
13. guideline.pt
14. exp guidelines/
15. practice guideline$.tw
16. exp practice guidelines/
17. position statement$.tw
18. practice parameter$.tw
19. practice standard$.tw
20. consensus development conference.tw
21. consensus statement.tw
22. state-of-the-art conference.tw
23. recommendation$.tw
24. association$.tw
25. societ$.tw
26. societies/
27. societies medical/
28. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
29. 24 or 25 or 26 or 27
30. 23 and 29
31. 28 or 30
32. 11 and 31
DIAGNOSIS
33. 11 and diagnosis.tw
34. 11 and imaging.mp
35. 11 and sonography.mp
36. 11 and ultrasonography.mp
37. 11 and tomography.mp
38. 11 and scintigraphy.mp
39. 33 or 34 or 35 or 36 or 37 or 38
TREATMENT
40. cryptorchidism/th
41. cryptorchidism/su
42. 11 and treatment.mp
43. gonadorelin/
44. 11 and 43
45. gonadotropin
46. 11 and 45
47. 40 or 41
48. limit 47 to human
49. limit 48 to (english or french or german or italian or spanish)
50. 44 or 46 or 49
51. limit 50 to review articles
52. limit 50 to guideline
53. limit 50 to meta-analysis
54. limit 50 to multi-center study
55. limit 50 to randomized controlled trial
56. limit 50 to review, academic
PROGNOSIS
57. 11 and prognosis.mp
58. 11 and complication$.mp
PUBLICATION DESIGN
59. 11 and controlled clinical trial.tw
60. 11 and placebo.tw
61. 11 and random$.tw
62. 11 and meta-anal$.tw
63. 11 and double-blind method/
64. 11 and double blind.tw

mal. Infertility was found in 10% of these patients vs. 6% in normal controls in paternity studies. There are no studies comparing treated with untreated unilateral cryptorchidism, but unilaterally absent testis or unilateral orchidectomy do not alter paternity rates [24].

Younger age at surgery is correlated with more favourable FSH and inhibin B levels later in life; whether this has an impact on fertility is not known, since early surgery has been advocated only in recent years. However, histological changes appear as early as 9 months of age, providing the rationale for early intervention in the hope of preventing further damage or even correcting these abnormalities [25].

Testicular growth is reportedly better if surgery is performed at 9 months than if performed at 3 years of age [26].

Risk for cancer incidence

The relative risk of testicular cancer in cryptorchid patients is about 5 times higher than in the general population [27]. 10% of all testicular malignancies are associated with cryptorchidism [28]. If the condition is treated before 10 years of age this risk may fall to almost normal [27], or at least be reduced to twice the norm [29]. However, seminoma, by far the most common type of cancer in cryptorchidism, has a survival rate of nearly 100% today, so that previous treatment of cryptorchidism has no impact on these patients' sur-

Table 2

Definitions of terms used to characterise cryptorchidism

Cryptorchidism:	Absence of at least one testicle in the scrotum
Gliding testis:	A testicle that can be brought down into the scrotum but does not stay there after release of the manipulation.
Retractile testis:	A testicle that comes to lie outside the scrotum because of the cremaster traction
Ectopic testis:	A really cryptorchid testis abnormally attached to extra-scrotal structures by gubernacular remnants [52, 53]
Ascending testis:	A testicle previously described as intrascrotal and that comes to lie permanently outside the scrotum, either primarily (abnormal involution of the peritoneo-vaginal process) or secondarily (post-surgery, trapped testis) [54–56].

Table 3

Summary of statements for the diagnosis and clinical management of cryptorchidism: quality of evidence, opinion of panel experts and strength of recommendations, where applicable.

Statement	Quality of evidence[1]	Strength of recommendations[2]	Opinion of panel experts about statement[3]
Diagnosis			
Cryptorchidism must be actively looked for at birth	Very low	Strong	Agree
Cryptorchidism must be actively looked for during routine pediatric controls	Very low	Strong	Agree
Cryptorchidism is best diagnosed clinically	Very low	Strong	Agree
Paraclinical examinations are not routinely needed	Very low	Strong	Agree
Clinical examination is performed with the patient supine	Very low	Uncertain	Agree
In case of doubt, the testes should be sought with the child sitting cross-legged	Very low	Uncertain	Agree
If no testis is palpable, genetic sex and hormonal status must be assessed	Very low	Strong	Agree
If cryptorchidism is associated with other signs of hypovirilisation such as hypospadias, genetic sex and hormonal status must be assessed	Very low	Strong	Agree
Laparoscopy is the best diagnostic approach to impalpable testes	Very low	Weak	Agree
The findings must be recorded in the patient's medical file	Very low	Strong	Agree
Treatment			
Spontaneous descent can be expected during the first semester of life	High	Strong	Agree
Optimal age for medical or surgical intervention is 6 to 12 months	Low	Uncertain	Agree
If the testis lies distal to the superficial inguinal pouch, treatment with human chorionic gonadotrophin may be tried	Low	Uncertain	Uncertain
If the testis lies distal to the superficial inguinal pouch, treatment with LH-RH-analogues may be tried	Low	Uncertain	Uncertain
Cryptorchidism should be treated by surgical orchidopexy	Moderate	Strong	Agree
The operation should be performed by specialised paediatric teams in order to minimize complications	Moderate	Weak	Agree
The rationale for treatment between 6 and 12 months is based on histological findings and data supporting better testicular growth after early surgery	Low	N/A	Agree
The rationale for treatment between 6 and 12 months is based on the absence of augmented surgical risk in experienced hands	Low	N/A	Agree
Routine biopsy is not needed	Low	Strong	Agree
Follow-up: Fertility			
In unilateral cryptorchidism paternity chances are close to those in the control population	High	N/A	Agree
In unilateral cryptorchidism sperm count abnormalities can be expected	High	N/A	Agree
In bilateral cryptorchidism impaired fertility must be expected	High	N/A	Agree
In bilateral cryptorchidism not corrected by the time of puberty paternity chances are very low	High	N/A	Agree
Follow-up: Oncological risk			
Testicular cancer risk in patients with cryptorchidism is 4–10 times higher than in the control population	High	N/A	Agree
Treatment performed before 10 years of age reduces the oncological risk to 1–2 times the norm	High	N/A	Agree
Testicular status should be periodically assessed by the physician throughout childhood in all patients with treated or untreated cryptorchidism	Very low	Uncertain	Agree
Adult patients with a history of cryptorchidism should be taught testicular self-palpation in order to discover any abnormality	Very low	Uncertain	Agree
Screening biopsy is not indicated	Low	Strong	Agree

[1] High / Moderate / Low / Very low

[2] Strong / Weak / Uncertain / Rejected / Not Applicable (N/A)

[3] Agree / Uncertain / Disagree with statement

vival [30, 31]. Systematic biopsy is not needed to detect malignant tissue or a pre-malignant condition.

Risk to psychosexual wellbeing

Many authors agree that a dystopic testis may interfere with psychosexual well-being [1]. Spermarche comes later in cryptorchid patients, but sexual activity, penis size, testosterone levels, impotency problems and masculine identity scores are the same as in the general population [32, 33]. The literature on the role of orthotopic gonads in neurotic disturbances is unfortunately very scant [34].

Risk of testicular torsion

There is no evidence that cryptorchidism is linked with increased occurrence of testicular torsion, although the belief is widely held [35, 36].

Diagnosis

The diagnosis of cryptorchidism is clinical. It should be performed by an experienced examiner in a quiet environment, to minimize the effect of the cremasteric reflex [31]. Spontaneous testicular descent can be expected only before 6 months of age [13, 32]. Retractile testes follow a completely different clinical course and are the main factor to consider in differential diagnosis of true cryptorchidism. Ascending testis accounts for a large proportion of late diagnoses of cryptorchidism. While some claim that pubertal testosterone production allows spontaneous descent [33], others object that histological changes and sperm count values are those of true cryptorchidism and that treatment is mandatory [34]. Testis location must be recorded in the patient's file in order to detect testicular ascent.

Bilaterally non-palpable testes or unilateral cryptorchidism associated with hypospadias suggest a disturbance of sexual differentiation and require endocrine and genetic work-up. To date, no imaging technique for non-palpable testes has proven superior to laparoscopy, which also allows treatment if there is a testis. Contralateral testicular size cannot be used as a predictor of monorchidism [35].

Gadolinum-enhanced MR fares best among imaging modalities, with an accuracy of almost 100% on small series [36, 37]. However, imaging would make sense only in ruling out the presence of testicular tissue with potential for malignant degeneration, which is not the case yet [38].

Treatment

True cryptorchidism is associated with testicular cancer, infertility and psychological distress. Correcting the condition before 10 years of age brings the cancer risk down to normal. Treatment in the second semester of life aims to prevent histological changes and is not associated with more complications in the hands of experienced paediatric surgical teams than when performed later in life [24]. There is, however, no proven effect on fertility in this approach as compared with surgery by two years of age, as previously recommended [32, 45]. In one study, unilateral cryptorchid testes operated on at 9 months grew better than non-operated testicles in the control group [26] and testicles operated on at 3 years of age [38].

Surgery is the cornerstone of treatment. Inguinal or high scrotal approaches have been largely used for palpable or even non-palpable testes [47]. Laparoscopy has become standard practice in the diagnosis and treatment of non-palpable testes [48, 49].

The success rates of the various hormonal treatments in eliciting testicular descent or as adjuvant or neo-adjuvant treatments are not consistent enough to allow evidence-based recommendations [50–54].

Complications

Surgical mortality is extremely rare, and morbidity is lowest if specialist paediatric teams perform surgery. Complication rates are not higher in children undergoing surgery before age 2 [55, 56]. The most troublesome complications include injury to the vas deferens and testicular vessels.

Follow-up

The surgeon should evaluate patients at 1, 6 and 12 months post-surgery. Routine biopsies are not indicated. After puberty, any testicular modification should be sought by formerly cryptorchid patients through self-palpation [57]. Testicular size is not a predictor of sperm concentration values or of paternity chances [26].

Discussion and conclusion

In the absence of existing clinical practice guidelines available for adaptation we developed them *de novo*. We conducted a systematic search of the literature which allowed us to develop guidelines that include a series of statements, all of them rated by a multidisciplinary panel of experts. These statements offer evidence-based arguments for the rational management of paediatric cryp-

torchidism. These guidelines are subject to some limitations, however. The level and quality of available evidence was in general low or very low with the exception of follow-up for fertility. A local panel of experts who were also influenced by the local context examined the proposed statements; thus, these guidelines should not be applied without investigating whether they are valid in another context or country. Updating of these guidelines is not fully ensured due to the limited resources available for this purpose in the producer organisation.

We propose that cryptorchidism is best diagnosed clinically and treated by surgical orchidopexy at the age of 6–12 months without routine biopsy. If no testis is palpable, or if other signs of hypovirilisation such as hypospadias are present, chromosomal sex and hormonal status must be assessed. Laparoscopy is the best way to diagnose and manage intra-abdominal testes. Finally, we urge researchers in this and related fields to improve the quality of the research produced.

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