Management of cryptorchidism in children: guidelines

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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

Summary

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.
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 [7]. The expected best type of design varied according to the key topics structuring the paragraphs, according to the key topics structuring the evidence did depend on the design of the study. Twenty-eight statements were developed. The experts agreed to develop them de novo. If the condition has been corrected the risk falls to 38% in paternity studies. Age at treatment has no impact on fertility. Low birth weight and prenatal exposure to hormonal disruptors or tobacco in either the mother or the father are associated with decreased testes, along with an update of the literature [11].

Results and comments

We did not find existing guidelines covering the same issues and thus had to de novo, we defined Delphi technique [9], further adapted to be used for the explicit rating of evidence grades or levels [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 ascertainment 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.

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-
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Table 1
Search strategy, as used in Medline / Ovid.

<table>
<thead>
<tr>
<th>CRYPTORCHIDISM</th>
<th>GUIDELINES</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
<th>PROGNOSIS</th>
<th>PUBLICATION DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cryptorchidism/</td>
<td>12. guideline$tw</td>
<td>33. 11 and diagnosis.tw</td>
<td>80. cryptorchidism/th</td>
<td>57. 11 and prognosis.mp</td>
<td>59. 11 and controlled clinical trial.tw</td>
</tr>
<tr>
<td>2. empty scrotum.tw</td>
<td>13. guideline.pt</td>
<td>34. 11 and imaging.mp</td>
<td>41. cryptorchidism/su</td>
<td>58. 11 and complication$mp</td>
<td>60. 11 and placebo.tw</td>
</tr>
<tr>
<td>3. undescended testis$tw</td>
<td>14. exp guidelines/</td>
<td>35. 11 and sonography.mp</td>
<td>42. 11 and treatment.mp</td>
<td></td>
<td>61. 11 and random$tw</td>
</tr>
<tr>
<td>4. maldescensus testis$tw</td>
<td>15. practice guideline$tw</td>
<td>36. 11 and ultrasonography.mp</td>
<td>43. gonadorelin/</td>
<td></td>
<td>62. 11 and meta-analysis</td>
</tr>
<tr>
<td>5. non-descended testis$tw</td>
<td>16. exp practice guidelines/</td>
<td>37. 11 and tomography.mp</td>
<td>44. 11 and 43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. ectopic testis$tw</td>
<td>17. position statement$tw</td>
<td>38. 11 and scintigraphy.mp</td>
<td>45. gonadotropin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. retractile testis$tw</td>
<td>18. practice parameter$tw</td>
<td>39. 11 or 34 or 35 or 36 or 37 or 38</td>
<td>46. 11 and 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. cryptorchis.tw</td>
<td>19. practice standard$tw</td>
<td></td>
<td>47. 40 or 41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8</td>
<td>20. consensus development conference.tw</td>
<td></td>
<td>48. limit 47 to human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. limit 9 to human</td>
<td>21. consensus statement.tw</td>
<td></td>
<td>49. limit 48 to (english or french or german or italian or spanish)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. limit 10 to (english or french or german or spanish or italian)</td>
<td>22. state-of-the-art conference.tw</td>
<td></td>
<td>50. 44 or 46 or 49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23</td>
<td>23. recommendation$tw</td>
<td>51. limit 50 to review articles</td>
<td>52. limit 50 to guideline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. association$tw</td>
<td>25. societi$tw</td>
<td>53. limit 50 to meta-analysis</td>
<td>54. limit 50 to multi-center study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. societies/</td>
<td>27. societies medical/</td>
<td></td>
<td>55. limit 50 to randomized controlled trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23</td>
<td>29. 11 and prognosis.mp</td>
<td></td>
<td>56. limit 50 to review, academic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29. 24 or 25 or 26 or 27</td>
<td>30. 23 and 29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. 23 and 29</td>
<td>31. 28 or 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. 11 and 31</td>
<td>33. limit 10 to (english or french or german or spanish or italian)</td>
<td></td>
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</tr>
</tbody>
</table>

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.

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

1 High / Moderate / Low / Very low
2 Strong / Weak / Uncertain / Rejected / Not Applicable (N/A)
3 Agree / Uncertain / Disagree with statement
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Risk to psychosexual wellbeing

Many authors agree that a dystopic testis may interfere with psychosexual well-being [1]. Spermatogenesis 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].

Gadolinium-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-
tortorchidism. 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 producing 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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