Systematic review and meta-analysis comparing outcomes following orchidopexy for cryptorchidism before or after 1 year of age

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Background: Current guidelines recommend orchidopexy for cryptorchidism by 12 months of age, yet this is not universally adhered to. The aim of this systematic review and meta-analysis was to compare outcomes between orchidopexies performed before and after 1 year of age.

Methods: MEDLINE and Embase were searched (September 2015) using terms relating to cryptorchidism, orchidopexy and the outcomes of interest. Studies were eligible for inclusion if they compared orchidopexy at less than 1 year of age (early) with orchidopexy at 1 year or more of age (delayed) and reported the primary outcome (testicular atrophy) or one of the secondary outcomes (fertility potential, postoperative complication, malignancy). Studies were excluded when more than 50 per cent of infants had intra-abdominal testes, or the population included infants with disorders of sexual differentiation. Additional studies were identified through reference list searching. Unpublished data were sought from the ORCHESTRA study investigators.

Results: Fifteen eligible studies were identified from 1387 titles. There was no difference in atrophy rate between early orchidopexy and delayed orchidopexy (risk ratio 0.64, 95 per cent c.i. 0.25 to 1.66; 912 testes). Testicular volume was greater (mean difference 0.06 (95 per cent c.i. 0.01 to 0.10) ml; 346 testes) and there were more spermatogonia per tubule (mean difference 0.47 (0.31 to 0.64); 382 testes) in infants undergoing early orchidopexy, with no difference in complication rate (risk ratio 0.68, 0.27 to 1.68; 426 testes). No study reported malignancy rate.

Conclusion: Atrophy and complication rates do not appear different between early and delayed orchidopexy, and fertility potential may be better with early orchidopexy. Imprecision of the available data limits the robustness of these conclusions.

Funding information
National Institute for Health Research, DRF/2015/08/076

Paper accepted 9 November 2017
Published online 5 February 2018 in Wiley Online Library (www.bjopen.com). DOI: 10.1002/bjs5.36

Introduction

Cryptorchidism affects between 2.4 and 5 per cent of live-born boys1–4. Undescended testes are known to be associated with an increased incidence of testicular malignancy and subfertility, even after orchidopexy5–10. Epidemiological evidence11 shows that the risk of testicular cancer is increased markedly when orchidopexy is delayed to 13 years of age. However, histological changes are evident in testicular biopsies from boys as young as 2 years10.

The current theory is that there is a short time frame between 3 and 6 months of age when the normal maturation of gonocytes into type A spermatogonia should occur, and this process is temperature sensitive12. During this process there is also apoptosis of germ cells, and it is postulated that these persistent undifferentiated germ cells may lead to malignancy in the long term13. The latest guidance from several professional associations14–17, including a recent British Association of Paediatric Urologists
(BAPU) consensus statement, recommends performing orchidopexy by 12 months of age. This guidance is not adhered to universally. A recent international survey18 of 122 paediatric surgeons and urologists found that around half of surgeons considered that the optimal age for orchidopexy should be slightly older. Reasons cited for delaying surgery until boys are older than 12 months were concerns about possible increased rates of postoperative testicular atrophy in younger children and the heightened awareness of possible adverse effects on neurodevelopment of general anaesthesia in very young children. Much of the evidence about effects of anaesthesia on the developing brain come from animal studies; however, there is an increasing body of research investigating possible effects in humans19–22.

A recent systematic review by Chan and colleagues23 found some evidence to support earlier orchidopexy. However, this review was limited in terms of utility for supporting the BAPU consensus statement, as it did not specifically examine the merits of using a 1-year age cut-off, and provided limited evidence in relation to the harms that may be associated with earlier orchidopexy. The aim of the present systematic review was therefore to build upon the work of Chan et al.23 by making a specific comparison of the outcomes associated with orchidopexy before or after 1 year of age, including both benefits and harms.

Methods

The review was conducted according to a prespecified protocol registered on the Prospero International Prospective Register of Systematic Reviews (CRD42016025930).

The population of interest for this review were boys without disorders of sexual differentiation who were identified as having unilateral or bilateral cryptorchidism, and for whom an orchidopexy was performed. The intervention of interest was orchidopexy performed before 1 year of age, with orchidopexy performed at 1 year of age or later as a comparator. The primary outcome was testicular atrophy, regardless of method of measurement, with secondary outcomes including fertility potential, testicular malignancy, neurodevelopmental outcomes, and surgical or anaesthetic complication (defined as any deviation from the usual, anticipated, postoperative course). Studies were therefore eligible for inclusion if they compared orchidopexy performed before 1 year of age with orchidopexy performed at or after 1 year of age in boys with either unilateral or bilateral cryptorchidism, and reported at least one outcome of interest. It was considered likely that the outcomes of interest would be reported using multiple different methods of measurement, at multiple different time points. As the intention of this review was to understand the current state of evidence, as opposed to drawing robust conclusions for management, the decision was made not to restrict eligibility of studies based on their use of a specific outcome measure. Meta-analysis was, however, performed only for studies reporting comparable outcome measures.

As it is believed that infants with intra-abdominal testes have worse outcomes than those with testes located in the inguinal canal or suprascrotal pouch, studies that assessed outcomes purely for infants undergoing treatment for intra-abdominal cryptorchidism were excluded from the review. Studies where there was a mixed population of infants were, however, included, if the majority of testes were in the inguinal canal or suprascrotal pouch. This decision was made, as it was considered that exclusion of all studies with a heterogeneous population would prevent the review from addressing its primary objective. To aid transparency of the comparability of the intervention and control groups, the authors sought to describe the testicular positions reported in each included study. Studies including infants with disorders of sexual differentiation were also excluded, as these children are likely to represent a different population to those without disorders of sexual differentiation.

Multiple search strategies were used to identify relevant articles from MEDLINE and Embase. The initial search was performed on 3 September 2015, and rerun on 15 December 2016 to confirm that no additional eligible articles had been published between the initial search and submission for publication. Search terms were identified from database thesauri and free text relating to cryptorchidism, orchidopexy and the outcomes of interest. Terms were combined using Boolean operators (Appendix S1, supporting information). All study designs, except expert opinion, were eligible for inclusion, and no limits were placed based on year of publication, language or geographical location. Hand-searching of reference lists from included manuscripts was undertaken to identify additional eligible studies.

All papers were reviewed for eligibility by two authors working independently. Discrepancies were resolved by discussion, with recourse to another author when necessary. Data were also extracted by two authors working independently, again with discrepancies resolved by discussion and recourse to another author if needed.

Additional data were sought from the ORCHESTRA study group. The ORCHESTRA study24 is a multicentre, international cohort study comparing atrophy rates in infants undergoing orchidopexy before 1 year of age with
infants undergoing orchidopexy at or after the age of 1 year. This study is known to have concluded data collection, but has not yet published its results.

As recommended by the Cochrane Collaboration, the quality of the body of evidence contributing to each outcome was assessed by means of Grading of Recommendations Assessment, Development and Evaluation (GRADE). A summary for each outcome, which could range from very low to high quality, was produced.

Statistical analysis

Mean differences were calculated for continuous variables using the inverse variance method. Risk ratios (RRs) were calculated for dichotomous variables using the Mantel–Haenszel method. Meta-analyses were performed using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Where studies reported continuous outcomes using mean(s.d.) value for subgroups of the intervention and control groups used in the present review, data from these subgroups were combined into one summary measure using Microsoft® Excel® for Mac™ 2011 version 14.7.4 (170508) (Microsoft, Redmond, Washington, USA).

Results

Included studies and quality of evidence

After removal of duplicates, 1387 titles were reviewed, with 1006 excluded at title review stage, 335 at abstract review and 34 on review of full papers (Table S1, supporting information). After hand-searching of the reference lists of the 12 eligible studies identified from database searching, a further three eligible studies were identified. In total, 15 published studies9,25–38 were included in the review (Fig. 1 and Table 1). Of the 15 papers, four by Kollin and co-workers25–28 were based on the same population of infants, and papers by Feyles et al.29 and Canavese and colleagues9,30,31 also had overlapping populations. There was one RCT reported in four studies25–28 at different time points, three prospective cohort studies30,32,33, one case–control study34, one retrospective cohort study nested within a larger case–control study35 and six retrospective cohort studies or case series9,29,31,36–38. A retrospective cohort study by Tasian et al.37 was also reported as a conference abstract39 containing data from 14 more participants than the full manuscript. As the abstract contained significantly less detail than the full manuscript, and was reporting the same population, it was not included in the review. Unpublished data from the ORCHESTRA study24 were included in the analysis of the primary outcome.
Table 1  Characteristics of included studies

| Reference | Setting and methodology | Age at orchidopexy | No. of testes* | No. of intra-abdominal testes† | Outcomes reported |
|-----------|--------------------------|--------------------|---------------|-------------------------------|------------------|
| Kogan et al.  | Prospective cohort | < 12 months | 12–46 months | 13 | 64 | 0 (0) | Postoperative complication, testicular atrophy, testicular retraction, anaesthetic complication, mean seminiferous tubule diameter, mean number of germ cells per tubule |
| Canavese et al. | Retrospective cohort study Single centre Recruit 1980–1990 | < 12 months | > 12 months | 84 | 832 | 65 (7.1) in entire cohort | Testicular morphology, percentage of testes with normal number of spermatogonia |
| McAleer et al. | Retrospective cohort study Single centre Recruit 1986–1990 | < 12 months | 1–16 years | 51‡ | 189‡ | 25 (9.3) in entire cohort | Fertility index (mean number of spermatogonia per tubule) |
| Lala et al. | Prospective cohort study Single centre Unclear overlap of population with Canavese study | < 12 months, with or without failed LH and HCG therapy | > 12 months, after failed LH and HCG therapy | 52 | 155 | Intervention group 14 (27) Control group 32 (20.6) | Descent rate with hormone therapy, hormone therapy side-effects, duration of surgery, anaesthetic complications, postoperative complications, tubular atrophy, Leydig cell atrophy, normal epithelial histology, tubular atrophy, number of spermatogonia and type Ad spermatogonia |
| Canavese et al. | Prospective cohort study Single centre Recruitment period not specified | < 12 months | 12–36 months | 82 (67) | 72 (60) | Unable to determine from graphical representation | Testicular morphology, number of spermatogonia and type Ad spermatogonia, tubular atrophy, Leydig cell atrophy, and testicular atrophy |
| Kollin et al. | RCT with significant methodological limitations | 9 months | 3 years | 66 (70)§ | 69 (79)§ | 0 (0) | Median volume increase in testicular size between birth and age 2 years, ratio of descended to undescended testis volume, testicular atrophy, reoperation |
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|-----------|-------------------------|------------------|---------------|-----------------|------------------|
|           |                         | Intervention     | Comparator    | Intervention    | Control          |
| Kollin et al.26 | Follow-up of Kollin et al.24; additional patients recruited | 9 months | 3 years | 67 (72) §§ | 72 (83) §§ | 0 (0) | Testicular growth from birth to age 4 years, ratio of descended to undescended testis volume |
| Park et al.34 | Case–control study Single centre Recruitment 1998–2001 | < 12 months | > 12 months | 20 (20) | 45 (45) | n.r. | Number of germ cells per tubule, interstitial peritubular fibrosis, mean tubular fertility index, germ cell count, testicular volume at surgery, mean tubular diameter, Sertoli cell index |
| Canavese et al.9 | Retrospective cohort study Single surgical centre Recruitment 1986–1991 | < 12 months | 12–24 months | 18 (13) | 18 (16) | Intervention group 1 (6) Control group 3 (17) | Testicular volume at surgery, testicular volume at follow-up, sperm count > 20 million/ml, normal total sperm count, highly motile spermatozoa, sperm motility |
| Tasian et al.27 | Retrospective cohort study Single centre Recruitment 1991–2001 | < 12 months | 12 months to 18 years | 274 patients in entire cohort | 45 (16-4) in entire cohort | Odds of germ cell depletion per month of age at operation, odds of Leydig cell absence, severity of fibrosis |
| Kollin et al.27 | Follow-up of Kollin et al.24; additional patients recruited and 8 non-randomized patients included in intervention group | 9 months | 3 years | 127¶ | 92¶ | Intervention group 22 (17-3) Control group 10 (11) | Mean testicular volume at surgery, Sertoli cells per 100 cords, germ cells per 100 cords, cord diameter, percentage interstitial tissue, serum FSH, LH, inhibin B and testosterone levels |
| Kollin et al.28 | Follow-up of Kollin et al.25 | 9 months | 3 years | (78)# | (85)# | n.r. (assumed the same as Kollin et al.25) | Testicular volume at follow-up |
| Van Brakel et al.35 | Retrospective cohort study nested within a case–control study of impact of cryptorchidism on markers of fertility | < 12 months | 12 months to 12 years | (8)** | (36)** | n.r. | Testicular volume at follow-up, serum LH, FSH, testosterone and inhibin B levels, sperm concentration |
Table 1 continued

| Reference | Setting and methodology | Age at orchidopexy | No. of testes* | Outcomes reported |
|-----------|-------------------------|-------------------|---------------|------------------|
| Carson et al. 36 | Retrospective cohort study | < 12 months | 64 | Testicular atrophy, postoperative complications |
| Feyles et al. 29 | Retrospective cohort study | < 12 months | 35 (27) | Testicular volume at surgery, testicular volume at follow-up, total sperm count > 15 million/ml, highly motile spermatozoa, normal sperm count (%), normal sperm motility (%) |
| ORCHESTRA study 24 | Prospective cohort study | < 12 months | 39 (39) | Postoperative testicular atrophy |

Values in parentheses are *number of infants and †percentage of total testes unless indicated otherwise. ‡A total of 268 testes were recruited, but only 240 were analysed in primary study owing to inadequacy of samples; §number of infants randomized, with number of testes available at first follow-up time point in parentheses; ¶number of testes per group clear, but number of infants in each group unclear; #exact numbers of patients and testes unclear as text differs from tables; **62 boys with cryptorchidism included and 53 healthy controls recruited, but number of infants in intervention and control groups not stated.

Of the included studies, four 24–26,32 did not include any infants with intra-abdominal testes, eight 9,27,29,31,33,36–38 had less than 50 per cent intra-abdominal testes in their cohort, and four studies 28,30,34,35 did not report the proportion of intra-abdominal testes.

The GRADE quality of evidence was assessed as very low for all reported outcomes. All bar one of the studies contributing to the outcomes were observational in nature, and therefore the maximum score that could be awarded was low-quality evidence. Each study was judged to have sufficient methodological limitations to warrant downgrading to very low-quality evidence. Limitations included unclear comparability of baseline populations between intervention and control groups, imprecision of study results due to their small size, limitations associated with retrospective study designs, and unclear influence of loss to follow-up. The one RCT 25 included in the review was judged as very low-quality evidence owing to a lack of allocation concealment, lack of blinding, unclear loss to follow-up and inclusion of non-randomized participants in the study.

Testicular atrophy

Five studies 24,25,30,32,36 reported postoperative atrophy rates, with different definitions of atrophy used. Kollin and colleagues 25 defined atrophy according to a reduction in ultrasound-measured testicular volume, Carson and co-workers 36 and the ORCHESTRA study 24 defined atrophy as greater than 50 per cent reduction in postoperative size compared with either preoperative examination or unaffected contralateral testis, and Canavese et al. 30 and Kogan et al. 32 did not define atrophy at all. Only four of these studies 24,30,32,36 were included in the meta-analysis, as Kollin and co-workers 25 reported atrophy rates only for the intervention group. In total, 912 testes were included in the meta-analysis; 197 orchidopexies were performed before 12 months of age, with four reported cases of atrophy (2.0 per cent), and 715 orchidopexies were performed after 1 year of age, with 35 cases of atrophy reported (4.9 per cent) (RR 0.64, 95 per cent c.i. 0.25 to 1.66) (Fig. 2).

Postoperative complications

Three papers 32,33,36 reported rates of postoperative complications as a grouped measure including testicular atrophy. However, as Lala and colleagues 33 reported complications only for the intervention group, data from this study were not included in the meta-analysis. Overall, of 77 orchidopexies performed before 1 year of age, five complications occurred (6 per cent), whereas 33 complications occurred...
reported the mean number of spermatogonia per tubule, contributing 84 testes to the intervention group and 298 to the control group. There were more spermatogonia per tubule in infants undergoing orchidopexy before 12 months of age than in those having orchidopexy at 12 months of age or later (mean difference 0.47, 95 per cent c.i. 0.31 to 0.64) (Fig. 4).

Three studies reported mean tubular diameter at time of study, contributing 154 testes to the intervention group and 201 to the control group. Tubular diameter in infants undergoing orchidopexy before 12 months of age was larger than that in the older children by a mean difference of 9.77 (95 per cent c.i. 2.58 to 16.96) μm (Fig. 5).

Four studies reported testicular volume at the time of surgery; however, two reported data from the same population of infants, and therefore data from the smaller of these was not used in the meta-analysis. Testicular volume at the time of surgery was reported for 182 testes in the intervention group and 164 in the control group. The mean difference in volume at the time of surgery was 0.06 (95 per cent c.i. 0.01 to 0.10) ml greater for the intervention group (Fig. 6).

Spermatogonia, tubular diameter and testicular volume at surgery

Studies reported multiple surrogate measures of fertility. The most common were mean number of spermatogonia per seminiferous tubule, mean tubular diameter and testicular volume at the time of surgery. Three studies reported the mean number of spermatogonia per tubule, contributing 84 testes to the intervention group and 298 to the control group. There were more spermatogonia per tubule in infants undergoing orchidopexy before 12 months of age than in those having orchidopexy at 12 months of age or later (mean difference 0.47, 95 per cent c.i. 0.31 to 0.64) (Fig. 4).

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Fig. 4 Forest plot comparing the number of spermatogonia per tubule in boys with cryptorchidism who underwent orchidopexy at less than 1 year of age with those who had the operation at or after the age of 1 year. An inverse-variance fixed-effect model was used. Mean differences are shown with 95 per cent confidence intervals.

Fig. 5 Forest plot comparing tubular diameter in boys with cryptorchidism who underwent orchidopexy at less than 1 year of age with those who had the operation at or after the age of 1 year. An inverse-variance random-effects model was used. Mean differences are shown with 95 per cent confidence intervals.

Fig. 6 Forest plot comparing testicular volume at surgery in boys with cryptorchidism who underwent orchidopexy at less than 1 year of age with those who had the operation at or after the age of 1 year. An inverse-variance fixed-effect model was used. Mean differences are shown with 95 per cent confidence intervals.
Testicular volume at follow-up

Testicular volume at follow-up was reported in five studies9,25,26,28,29. Kollin and colleagues conducted an RCT in which infants were randomized at 6 months of age to orchidopexy at either age 9 months or 3 years. In a series of three manuscripts25,26,28, published in 2006, 2007 and 2013, they reported testicular size in both the intervention and control groups at different ages. In the 2006 report25, boys in the delayed surgery group were still preoperative. In the 2007 report26, both the early and delayed surgery groups were postoperative, and it was found that orchidopexy at 9 months of age resulted in a statistically significantly larger testis at age 4 years than when orchidopexy was performed at age 3 years. The data, however, are reported as median (i.q.r.) values, and therefore cannot be subjected to meta-analysis.

In their final 2013 report, Kollin et al.28 followed the same cohort of children up to age 5 years; boys who had undergone orchidopexy at 9 months of age had a statistically significantly larger testis at age 5 years than those who had orchidopexy at the age of 3 years. Canavese and co-workers9 and Feyles et al.29 did not find any difference in mean testicular volume between the early and delayed surgery groups at follow-up. These studies, however, were both significantly smaller than that of Kollin et al., and followed the children through into adulthood rather than stopping follow-up at age 5 years. Both of these studies9,29 drew data from the same population of children, and the Feyles study29 was the larger of the two. Given that these two papers reported on the same population, and their average age at follow-up was different from that of the Kollin cohort28 by approximately 15 years, meta-analysis was not performed. It was not possible to meta-analyse data reported in either of the other studies25,26, so no summary measure has been produced for testicular volume at follow-up.

Other fertility outcomes

Both Canavese and colleagues31 in 1993 and Feyles and co-workers29 in 2014 reported that boys undergoing orchidopexy before 1 year of age were more likely to have a normal total sperm count in later life than those having orchidopexy at or after age 1 year. In 2009, Canavese et al.9 reported that infants undergoing orchidopexy before the age of 1 year had a higher total sperm count, which was more likely to be greater than 20 million per ml in later life than boys undergoing orchidopexy at or after 1 year of age. All three studies9,29,31, however, drew data from the same population of infants; therefore, the results are not independent and meta-analysis was inappropriate.

Other fertility-related outcome measures reported in eligible studies include the number of spermatogonia per tubule (fertility index)38, percentage of tubules containing at least one germ cell amongst 50 randomly selected tubules, mean number of Sertoli cells per 50 randomly selected tubules, mean tubular diameter34, number of Sertoli cells per 100 tubules, number of germ cells per 100 tubules27, tubular atrophy30 and sperm motility29. Although many of these measures are reported to be better in infants undergoing orchidopexy before 1 year of age, there was such heterogeneity that meta-analysis to summarize them was not possible.

Other outcomes

There were no studies reporting outcomes directly relating to malignancy or neurodevelopment.

Discussion

This systematic review and meta-analysis comparing outcomes following orchidopexy before 1 year of age with outcomes following orchidopexy at or after the age of 1 year for cryptorchidism included 15 published studies and data from one unpublished study. Seven of the published studies were drawn from the same two populations of infants, and the quality of evidence provided for all reported outcomes was graded as very low. Four studies24,30,32,36 including912 testes contributed data to analysis of the primary outcome, testicular atrophy, with no difference in rates seen between boys who underwent orchidopexy before 1 year of age and those who had orchidopexy at or after 1 year of age.

There was also no evidence of difference in overall rates of postoperative complications between the two groups. Meta-analysis of secondary outcomes relating to fertility suggested that boys who underwent orchidopexy before 1 year of age had a statistically significantly larger testicle at the time of orchidopexy, significantly larger-diameter seminiferous tubules, and a significantly higher number of spermatogonia per seminiferous tubule than those who had orchidopexy at or after 1 year of age. Although not suitable for meta-analysis, other markers of fertility potential reported in eligible studies also appeared to suggest greater fertility potential in infants who underwent orchidopexy before 1 year of age.

These results therefore suggest a potential benefit of performing orchidopexy before 1 year of age, with no current evidence of additional harm. These results must, however, take into consideration the robustness of the primary data included in the review.

Although robust methodology was used in the design of this study, there are multiple limitations that affect
interpretation of the findings. First, no limits were placed on the age at which orchidopexy at or after 1 year of age could be performed, making the control group particularly heterogeneous. Further heterogeneity was introduced as boys with intra-abdominal cryptorchidism and those who had undergone hormonal therapy before orchidopexy were included in the review. Distribution of these children amongst the control and intervention groups was not always clearly described, making it difficult to interpret how these factors may have confounded the review’s results. Patient flow and study methodology were also unclear in many of the included studies, making it difficult to assess the impact of loss to follow-up and potential chance, confounding and bias on the results of the review.

Given the heterogeneity in choice of outcome measures relating to measures of fertility potential, it was impossible to produce one summary measure of fertility potential. It is therefore possible that the results of the meta-analyses do not reflect the true picture. Each of the fertility measures assessed is also only a surrogate for true fertility, and although some, such as sperm count and morphology, have been correlated with fertility, others, including testicular volume, number of germ cells present on testicular biopsy and testicular histology at the time of operation, have a less certain relationship. It is therefore impossible, from the studies included in this review, to draw any direct correlations between performing orchidopexy before 1 year of age and improved fertility.

A previous systematic review by Chan and colleagues summarized the evidence relating to the impact of age of orchidopexy on testicular malignancy and fertility potential. Their conclusion was that the optimal time to perform orchidopexy was between 6 and 12 months of age, as this was considered to maximize fertility potential and minimize malignancy risk, whilst also allowing for the spontaneous descent of the cryptorchid testis, which is reported to occur most commonly before the age of 6 months. Their review was, however, broad in its scope, looking at general trends in the impact of age on outcome, as opposed to exploring the impact of performing orchidopexy before a specific age cut-off. The results of the present review are in broad agreement with those of Chan et al., but it provides additional information relating to the safety of orchidopexy before 1 year of age. Neither review, however, has been able to comment on the safety of delivering anaesthesia for orchidopexy before the age of 1 year, with the best evidence in this area being provided instead by the GAS (General Anaesthesia compared to Spinal) trial. This is a large, high-quality RCT comparing sevoflurane anaesthesia with awake spinal anaesthesia for inguinal herniotomy in infants with gestational age at birth of more than 26 weeks and postmenstrual age at operation of less than 60 weeks. The trial is still to report on its primary outcome of IQ scores at 5 years of age, but the secondary outcome of performance on Bayley Scales of Infant and Toddler Development at 2 years of age has shown no difference between general anaesthesia and awake spinal anaesthesia. The type and duration of general anaesthesia delivered for an inguinal herniotomy is likely to be similar to that required for an orchidopexy.

The results of this systematic review and meta-analysis suggest that there is currently insufficient evidence to advocate a wholesale move to performing all orchidopexies before 1 year of age, but there is some evidence that this may improve fertility potential. Given the equivocal state of the available evidence, in order to support the BAPU consensus statement, high-quality RCTs must be conducted. These trials must assess harms as well as benefits, and also document the rates of spontaneous testicular descent seen in the delayed intervention group. Significant preliminary work must, however, be completed before attempting such RCTs. This will include identification of an appropriate, reliable, non-invasive surrogate marker of fertility, and establishment of mechanisms for linking study participants to cancer registries or routinely collected data in order to identify long-term risk of malignancy. Results from such an RCT could be combined with the final results of the GAS study to provide the robust evidence required either to support or to refute the BAPU consensus statement.

Acknowledgements

E.D. and D.F.-C. contributed equally to this publication. B.S.R.A. is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship. D.F.-C. is supported by the NIHR Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford. The views expressed are those of the author(s) and not necessarily those of the National Health Service, NIHR or Department of Health. The NIHR had no role in the design or conduct of the study; collection, management, analysis or interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

Disclosure: The authors declare no conflict of interest.

References

1 Thonneau PF, Gandia P, Mieusset R. Cryptorchidism: incidence, risk factors, and potential role of environment; an update. J Androl 2003; 24: 155–162.
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2 Cortes D, Kjellberg EM, Breddam M, Thorup J. The true incidence of cryptorchidism in Denmark. J Urol 2008; 179: 314–318.
3 Toppari J, Kaleva M. Maldescend testis. Horm Res 1999; 51: 261–269.
4 John Radcliffe Hospital Cryptorchidism Study Group. Cryptorchidism: a prospective study of 7500 consecutive male births, 1984–8. Arch Dis Child 1992; 67: 892–899.
5 Giwercman A, Bruun E, Frimodt-Møller C, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. J Urol 1989; 142: 998–1001.
6 Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. World J Urol 2004; 22: 2–14.
7 Kaplan G, Roswit B. Bilateral testicular tumors following bilateral orchiopexy. J Am Med Assoc 1970; 144: 1557–1558.
8 Murphy F, Paran TS, Puri P. Orchidopexy and its impact on fertility. Pediatr Surg Int 2007; 23: 625–632.
9 Canavese F, Mussa A, Manenti M, Cortese MG, Ferrero L, Tuli G et al. 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 2009; 19: 388–391.
10 Hadziselimovic F, Herzog B. The importance of both an early orchidopexy and germ cell maturation for fertility. Lancet 2001; 358: 1156–1157.
11 Pettersson A, Richiardi L, Nordenskjöld A, Kajiser M, Akre O. Age at surgery for undescended testes and risk of testicular cancer. N Engl J Med 2007; 356: 1835–1841.
12 Hutson JM. Journal of Pediatric Surgery-Sponsored Fred McLeod Lecture. Undescended testes: the underlying mechanisms and the effects on germ cells that cause infertility and cancer. J Pediatr Surg 2013; 48: 903–908.
13 Hutson JM, Li R, Southwell BR, Petersen BL, Thorup J, Cortes D. Germ cell development in the postnatal testis: the key to prevent malignancy in cryptorchidism? Front Endocrinol (Lausanne) 2012; 3: 176.
14 Ritzén EM, Bergh A, Bjernes R, Christiansen P, Cortes D, Haugen SE et al. Nordic consensus on treatment of undescended testes. Acta Paediatr 2007; 96: 638–643.
15 Radmayr C, Dogan HS, Hoebeka P, Koecvara R, Nijman R, Stein R et al. Management of undescended testes: European Association of Urology/European Society for Paediatric Urology Guidelines. J Pediatr Urol 2016; 12: 335–343.
16 Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY et al.; American Urological Association. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014; 192: 337–345.
17 British Association of Paediatric Urologists (BAPU). UDT Consensus Document; 2013. http://www.bapu.org.uk/udt-consensus-statement/ [accessed 4 December 2017].
18 Bradshaw C, Skerritt C, Hall NJ, Woodward M, McCarthy L, PSTRN (eds). Yet to Reach a Consensus? Consultants’ Attitudes to the Ideal Age for Orchidopexy. British Association of Paediatric Surgeons Annual Congress, 2015.
19 Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zoruzmni CF et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003; 23: 876–882.
20 Raper J, Alvarado MC, Murphy KL, Baxter MG. Multiple anesthetic exposure in infant monkeys alters emotional reactivity to an acute stressor. Anesthesiology 2015; 123: 1084–1092.
21 Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity – clinical implications of animal models. N Engl J Med 2015; 372: 796–797.
22 Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G et al.; GAS consortium. Neurodevelopmental outcome at 2 years of age after general anaesthesia and wake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2016; 387: 239–250.
23 Chan E, Wayne C, Nasr A; FRSCS for Canadian Association of Pediatric Surgeon Evidence-Based Resource. Ideal timing of orchidopexy: a systematic review. Pediatr Surg Int 2014; 30: 87–97.
24 Paediatric Surgery Trainees Research Network (PSTRN). ORCHESTRA Protocol Version 1; 2014. http://pstrn.org.uk/wp-content/uploads/2014/06/ORCHESTRA-protocol-v1-Jun-14-2014.pdf [accessed 4 December 2017].
25 Kollin C, Hesser U, Ritzen EM, Karpe B. Testicular growth from birth to two years of age, and the effect of orchidopexy at age nine months: a randomized, controlled study. Acta Paediatr 2006; 95: 318–324.
26 Kollin C, Karpe B, Hesser U, Granholm T, Ritzen EM. Surgical treatment of unilaterally undescended testes: testicular growth after randomization to orchidopexy at age 9 months or 3 years. J Urol 2007; 178(Suppl): 1589–1593.
27 Kollin C, Stuenkendorf JB, Nurmio M, Sundqvist E, Gustafsson T, Soder O et al. Boys with undescended testes: endocrine, volumetric and morphometric studies on testicular function before and after orchidopexy at nine months or three years of age. J Clin Endocrinol Metab 2012; 97: 4588–4595.
28 Kollin C, Granholm T, Nordenskjöld A, Ritzen EM. Growth of spontaneously descended and surgically treated testes during early childhood. Pediatr Res 2013; 131: e1174–e1180.
29 Feyles F, Peiretti V, Mussa A, Manenti M, Canavese F, Cortese MG et al. [Improved sperm count and motility in young men surgically treated for cryptorchidism in the first year of life.] Eur J Pediatr Surg 2014; 24: 376–380.
30 Canavese F, Cortese MG, Magro P, Lonati L, Teruzzi E, De Sanctis C et al. Cryptorchidism: medical and surgical treatment in the 1st year of life. Pediatr Surg Int 1998; 14: 2–5.
31 Canavese F, Lalla R, Linari A, Cortese MG, Gennari F, Hadziselimovic F. Surgical treatment of cryptorchidism. Eur J Pediatr 1993; 152(Suppl 2): S43–S44.
32 Kogan SJ, Tennenbaum S, Gill B, Reda E, Levitt SB. Efficacy of orchiopexy by patient age 1 year for cryptorchidism. *J Urol* 1990; **144**(Pt 2): 508–509.

33 Lala R, Matarazzo P, Chiabotto P, Gennari F, Cortese MG, Canavese F *et al.* Early hormonal and surgical treatment of cryptorchidism. *J Urol* 1997; **157**: 1898–1901.

34 Park KH, Lee JH, Han JJ, Lee SD, Song SY. Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis. *Int J Urol* 2007; **14**: 616–621.

35 van Brakel J, Kranse R, de Muinck Keizer-Schrama SM, Hendriks AE, de Jong FH, Bangma CH *et al.* Fertility potential in men with a history of congenital undescended testes: a long-term follow-up study. *Andrology* 2013; **1**: 100–108.

36 Carson JS, Cusick R, Mercer A, Ashley A, Abdessalam S, Raynor S *et al.* Undescended testes: does age at orchiopexy affect survival of the testis? *J Pediatr Surg* 2014; **49**: 770–773.

37 Tasian GE, Hittelman AB, Kim GE, DiSandro MJ, Baskin LS. Age at orchiopexy and testis palpability predict germ and Leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. *J Urol* 2009; **182**: 704–709.

38 McAleer IM, Packer MG, Kaplan GH, Scherz HC, Krous HF, Billman GF. Fertility index analysis in cryptorchidism. *J Urol* 1995; **153**: 1255–1258.

39 Tasian GE, Hittelman A, Kim GE, DiSandro MJ, Baskin LS. Cryptorchidism and male fertility potential: clinical predictors of adverse histological features. *J Urol* 2009; **1**: 119.

40 Bostofte E, Serup J, Rebbe H. Relation between sperm count and semen volume, and pregnancies obtained during a twenty-year follow-up period. *Int J Androl* 1982; **5**: 267–275.

41 Bonde JP, Ernst E, Jensen TK, Hjollund NH, Kolstad H, Henriksen TB *et al.* Relation between semen quality and fertility: a population-based study of 430 first-pregnancy planners. *Lancet* 1998; **352**: 1172–1177.

42 Lenz S, Giwercman A, Elsborg A, Cohr KH, Jelnes JE, Carlsen E *et al.* Ultrasonic testicular texture and size in 444 men from the general population: correlation to semen quality. *Eur Urol* 1993; **24**: 231–238.

43 Takihara H, Cosentino MJ, Sakatoku J, Cockett AT. Significance of testicular size measurement in andrology: II. Correlation of testicular size with testicular function. *J Urol* 1987; **137**: 416–419.

44 Noh PH, Cooper CS, Snyder HM III, Zderic SA, Canning DA, Huff DS. Testicular volume does not predict germ cell count in patients with cryptorchidism. *J Urol* 2000; **163**: 593–596.

45 Lee PA, Coughlin MT, Bellinger MF. No relationship of testicular size at orchiopexy with fertility in men who previously had unilateral cryptorchidism. *J Urol* 2001; **166**: 236–239.

46 Hamza AF, Elrahim M, Elnagar, Maaty SA, Bassiouny E, Jehannin B. Testicular descent: when to interfere? *Eur J Pediatr Surg* 2001; **11**: 173–176.

Additional supporting information can be found online in the supporting information tab for this article.
**Graphical Abstract**

The contents of this page will be used as part of the graphical abstract of HTML only. It will not be published as part of main article.

| Reference          | Testicular atrophy | Weight (%) | Risk ratio |
|--------------------|--------------------|------------|------------|
| Kogan et al.       | <12 months         | 7.5        | 0.93 (0.05, 18.30) |
| Carson et al.      | ≥12 months         | 0.05       | 0.56 (0.17, 1.79)  |
| Carson et al.      | ≥12 months         | 0.21       | Not estimable   |
| ORCHISTRA study    | ≥12 months         | 0.92       | 0.86 (0.11, 6.60)  |
| Total              |                    | 17.5       | 0.64 (0.25, 1.66)  |

Current guidelines recommend orchidopexy for cryptorchidism by 12 months of age, yet this is not universally adhered to. This systematic review and meta-analysis found no difference in testicular atrophy and operative complication rates between orchidopexy performed before or after 12 months of age, while fertility potential may be better with early orchidopexy. Imprecision of the available data limits the robustness of these conclusions.