Author’s response to reviews

Title: Analysis of the association between paternity and reoperation for urethral obstruction in adult hypospadias patients who underwent two-stage repair in childhood

Authors:

Akihiro Kanematsu (aqui@hyo-med.ac.jp)
Shiro Tanaka (tanaka.shiro.8n@kyoto-u.ac.jp)
Takahiko Hashimoto (th-uro@hyo-med.ac.jp)
Michio Nojima (nojimam@hyo-med.ac.jp)
Shingo Yamamoto (shingo@hyo-med.ac.jp)

Version: 2 Date: 29 Jun 2019

Author’s response to reviews:

To Editor

BMC Urology

June 29, 2019

Dear Editor

I, along with my coauthors, submit a revised version of the attached manuscript of an original article entitled “Analysis of the association between paternity in adult hypospadias patients and reoperation for urethral obstruction after two-stage repair during childhood” for BMC Urology

We made responses to all the critiques made upon initial version, and incorporated them to the revised manuscript. We appreciate the times Reviewers have taken for this manuscript, which have significantly improved contents of the article.

We attached point-to-point response and excerpt of amendment made on the manuscript according to each comment made by the reviewers.
Response to Dr Ali M. Ziada (Reviewer 1):

Comment

The authors present an interesting idea however it was lacking on execution. The authors operate under the assumption that strictures and obstructive factors were the most important reasons for delayed paternity. Unfortunately this is a missed opportunity that the authors did not review all applicable parameters. I was unable to see what questions the questionnaire included but I would argue that not only strictures would be to blame but it would be interesting to look at degree of hypospadias, degree of curvature if measured before and after, quality of the ejaculate in severe cases, self esteem with repeated surgeries my predispose to lack of confidence to pursue relationships.

How many had curvature that led to intercourse problems?

Response

We appreciate the Reviewer’s comment.

1. Degree of hypospadias has been included in multivariate analysis of our pervious article, and had significant impact for sexual intercourse, but not on paternity. Indeed, as shown in Table 2 the degree of hypospadias was equivalent between the Control and Study groups (P=1.00). No amendment was made on this issue.

2. We do not have objective data on past and present penile shape, as stated as the study limitation in the revised manuscript, but question about present curvature has been asked to the patients as the problems with penile shape (shown as Q17-1 in revised Appendix). The problem of bending was documented by 9/78 (11.5%) in control, and 1/11 (9.0%) in study (P=0.78, not significant), and it was included in the revised Table 3.

3. If the word ‘quality of the ejaculate’ means semen quality, we do not have concrete seminalysis data, as has been stated as study limitation in the initial version. We added the description about quality of ejaculation (drawn from responses to Q29 in Appendix), as rate of the patients who actually reported weak or incomplete ejaculation, which was again significant and added in the revised Table 3.

4. For patients’ self-esteem, we added the response to the question asking hesitation before and after first sexual intercourse (shown as Q30 and Q31-4 in revised Appendix), which was not significant, added in the revised Table 3.

5. We described about the answer for Q31-6 (newly added to Appendix) in revised Figure 3. Only 1 case in Control group complained for bending as cause of problem for intercourse, and none in Study group patients.
Amendments

Results

(P15L6) ‘The problem of bending was documented by 9/78 (11.5%) in control, and 1/11 (9.0%) in study (P=0.78, not significant). It was problematic for sexual intercourse in only one patient in Control group.’

(P14L4) ‘Although the Study group patients tended to marry older, hesitation before and after the first intercourse was not significantly higher than the Control.’

(P15L12) ‘specifically for weak or incomplete ejaculation (66.7% vs. 15.6%, p=0.0017.’

Discussion

(P18L5) ‘Mureau et al reported that, the later the patients underwent surgery, the greater were their inhibitions in seeking sexual contact and the later they made the first sexual contacts.[18] However, between the patients reoperated for obstructive of non-obstructive cause, the timing of the first and last reoperation was not statistically significant, nor was the age of first intercourse.’

Intercourse.

(P19L14) ‘However, we lack the seminalysis, uroflow, and concrete penile shape data, which is a major limitation of our study,’

References


Appendix

Q17-1 If yes, what is the reason for your dissatisfaction?

1. Phimosis
2. Lack of prepuce
3. Too small size
4. Too large size
5. Position of meatus
6. Penis itself
7. Shape of the glans
8. Presence of scar
9. Color of the Penis
10. Bending of the penis
11. Hair of the penis
12. Others (Please specify )

Q30 Before you experienced sexual intercourse, have you felt hesitation for sexual activity because of your penile shape?
1. Yes 2. No

Q31-4 After you experienced sexual intercourse, have you felt hesitation for sexual activity because of your penile shape?
1. Never
2. Hesitation has disappeared
3. Hesitation persists
4. Hesitation became worse

Q31-6 If you answered ‘Yes’ to Q31-5, what is the problem for intercourse.
1. Penis is not rigid enough
2. Erection does not persist
3. Pain during intercourse (=sex)
4. Others (Please specify )

Table 3 has new rows describing
Penile bending
Intercourse
Difficult intercourse for penile bending
Ejaculation
Weak or incomplete ejaculation

Hesitation for intercourse
Before first intercourse
After first intercourse

Comment
Also the study had a very high reoperation rate for distal cases which the authors did not elaborate on.

Response
We did not discuss whether reoperation rate for the distal cases were high or not, because the mildest cases were treated by one-stage repair like MAGPI. Glandular and penile type cases in this study may have undergone 2 stage repair, because they were judged to have bending that needed correction, at least by the surgeon of this series. Therefore, we avoided the word ‘distal’ and replaced it by ‘mild’.

Amendment
Out of 108 patients in our earlier study, we selected out 90 patients who underwent a two-stage repair by a single surgeon from mild to severe type of hypospadias.

Comment
It would be also interesting to find out what was the number of patients in an active relationship and desiring paternity.

Response
We completely agree to the Reviewer’s comment, but cannot answer it because these points were not included in the questionnaire. Therefore, we avoided the word ‘fertility’, which should be reserved for those who wish to have child.

(P18L4,L7) fertility -> paternity
Response to Dr Kimihiko Moriya (Reviewer 2):

Comment

The authors presented the long-term outcome of hypospadias surgery with special emphasis on paternity based on the questionnaire study. They demonstrated that history of reoperation for urethral obstruction was associated with lower paternity rate. This finding was interesting, however, the number of patients with urethral obstruction was unfortunately too small especially those under marriage to confirm this finding.

Response

We appreciate the Reviewer’s comment and critique. Indeed, our finding should be tested in the future study in larger population, which is another limitation of the study. This point has been already addressed in the initial manuscript, but we made further modification to emphasize the point.

Amendment

Abstract

(P3L14) ‘although it should be further tested in the future for larger groups of hypospadias patients.’

Discussion

(P20L16) ‘Since our data derive from limited number of patients, with 12 Study group patients without offspring, of which only 5 were married, our findings should be further tested by future study by different groups and by ourselves.’

(P22L1) ‘The findings in this report may suggest that reoperation for urethral obstruction was associated with lower paternity, but because of the limited number of Study patients, it should be further tested by the future studies in larger groups of hypospadias patients.’

Comment

1. This kind of questionnaire based study is prone to be biased between responders and non-responders. To generalize the outcome of this study, responders should be a representative cohort of each group. Did authors evaluated the background of the patients between responders and non-responders with stratification of each group?
Response

In our previous study, we reported that, distribution of hypospadias type was not statistically different between responders and no responders who received the mail. So was type of initial repair they received. We described that,

(P16L6 no amendment made) ‘Among the 518 mailed patients with the exclusion of 80 cases in which operative procedure was not identified, 81.2% (358/438) underwent the same two-stage repair, which is equivalent to 83.3% (90/108) of the present and previous studies. This may indicate that our responders represent the total patient group treated during that period without significant selection bias with regard to the operation procedure.’

(P20L10 no amendment made) ‘Limited response can cause selection bias, but we would like to note that there was no significant difference in background between the responders and non-responders with respect to hypospadias severity as reported in the previous study[14] and the type of initial repair procedure as described in this report.’

Comment

2. Was the age of partner of patients with marriage asked? Since the age of marriage was later in the Study group, the age of their partner would be higher.

Response

Unfortunately, the age of the partner was not included in the questionnaire, but higher age of partner could be a reason for less paternity rate. We appreciate the Reviewer’s suggestion and included the point in the revised manuscript.

Amendment

(P19L6) ‘As another point, a later marriage may have reduced the child-bearing period, presumably having more aged partner than those who married earlier.’

Comment

3. As authors pointed out, age at marriage was significantly higher in Study group than Study control. That would be one of the reasons for the difference in paternity rate. When the age at marriage was matched between both groups, was paternity rate different?
Response

We calculated data of the patients married at older age (>28). Paternity rate of the Control patients became lower than in Figure 4D, but was still higher than in Study patients. Because of small number in both Control and Study groups (N=8 vs. N=4) we did not believe it worth presenting.

Comment

4. In figure 3, each curve meant total reoperation rate, reoperation rate for non-obstructive complication, reoperation rate for obstructive complication. Figure 3 demonstrated that timing of reoperation after initial surgery was similar between patients with obstructive and non-obstructive reason. Was the age at reoperation also similar? Mureau et al (J Urol 154, 1351-1355, 1995) reported "An important factor affecting psychosexual adjustment seems to be the age at which surgery was completed. The later the patients underwent surgery, the greater were their inhibitions in seeking sexual contacts and the later they made the first sexual contacts."

Response

We appreciate for a constructive suggestion. The age of the last reoperation was not significantly different, 13.8±8.2 in Study group, and 9.6±5.5 in patients reoperated for non-obstructive cause, and we added the description in Results. The point raised by Mureau et al. should be important, but it may not be applicable to our patients, in which age of first intercourse was not different between Study group and the Control group. Also, according to questionnaire, hesitation before and after the first experience of intercourse was not different between Control and Study groups.

Amendment

Results

(P12L8) ‘The age of the last reoperation was 13.8±8.2 y for those who had obstructive complications, and 9.6±5.5 y for those who had non-obstructive complications (p=0.063).’

(P14L4) ‘Although the Study group patients tended to marry older, hesitation before and after the first intercourse was not significantly higher than the Control.’

Discussion

(P18L5) Mureau et al reported that, the later the patients underwent surgery, the greater were their inhibitions in seeking sexual contact and the later they made the first sexual contacts.[18] However, between the patients reoperated for obstructive or non-obstructive
cause, the timing of the first and last reoperation was not statistically significant, nor was the age of first Intercourse.

References


Comment

6. Were the patients regularly followed after surgery? If so, until when? Was functional evaluation using uroflowmetry performed? or symptom-based follow-up? If evaluation of urethral obstruction was indicated based on symptoms, there may be some patients in Study control who had similar degree of urethral obstruction with patients in Study group.

Response

The patients have been followed for indefinite years, mainly based upon symptoms, without regular uroflowmetry. They were not discharged from regular outpatient follow up, but most of them ceased hospital visits by their own decision. We agree to the Reviewer’s point, and consider that lack of uroflowmetry data is a major limitation of the paper. Since this point has been already addressed in the initial manuscript, we did not make further change, but just cite the sentence here.

(P20L13 no amendment made) ‘Another limitation is that the majority of the information regarding the present condition of the participants was obtained through a survey, and there is a lack of objective data, such as seminalysis or uroflowmetry.’

Response to Dr Bruce Schlomer (Reviewer 3):
Comment

Introduction

1. I would add to 1st paragraph that long term consequences in patients with unrepaired hypospadias is unclear as well. The natural history of untreated hypospadias, especially mild cases, is unclear and could have a mostly benign course.

Response

We appreciate the Reviewer’s point and included additional sentences, with a new citation.

Amendments

Introduction

(P5L3) ‘The natural history of mild hypospadias is unclear but could have a mostly benign course without treatment.[1] However, patients with more severe hypospadias undergo repair during infancy, in the hope that with corrected penis, the patient will subsequently have a normal reproductive function as a male’

References


Comment

2.Did the authors have a hypothesis? Presumably, they hypothesized that those who had obstructive complications after 2 stage repair had lower paternity. This should be stated clearly.

Response

We appreciate the Reviewer’s point and modified the last sentence to state our hypothesis more clearly.
Amendment

(P6L13) ‘We hypothesized that reoperation for urethral obstruction after initial hypospadias repair could be related with decreased paternity, and aimed to clarify the association between them.’

Comment

Methods

1. I find it surprising that 2 stage repairs were performed for almost all hypospadias cases over 25 years. This would make these results not applicable to most institutions.

Response

Our institute introduced TIP repair in 1999, which was not quite late from initial report by Dr Snodgrass in 1996. The patients treated thereafter have just entered adulthood, which may be the same for the most other institutions and are still too young for asking about paternity. Results of older procedures can be compared with future result of current procedures.

Amendment

We deleted the description that this report could be used as a reference for other studies.

Comment

2. How was the glandular urethra created? Was this with a flap? A graft? This needs to be explained.

Response

Glandular urethra was created by inverted preputial flap.

Amendment

(P7L10) ‘In the first stage, the chordee tissue surrounding the penile shaft was completely removed and glandular urethra was created by inverted preputial flap.’
Comment

3. The authors compared the group who had surgery for obstruction to all other cases from their institution as well as to the general public. Is this comparison to general public data valid? Can the authors provide references on the method they used for this? Perhaps other studies have done similar comparisons using this dataset? Did the authors obtain a complete dataset from which they could perform log rank testing and survival curve analysis or did they just use the mean with SD to create a z-score? From what I can tell, the authors just put a mark on the failure curves for different ages.

Response

The general public data was obtained from a national survey on marriage and delivery by the Japanese government. The national survey provides the most valid control which represents the entire (age-specific) population in Japan. The subjects in the national survey were selected two-stage stratified random sampling; at the first stage, approximately 1000 geographic areas were randomly sampled, and at the second stage, all single persons and married women were selected as the subjects. In the statistical analysis of our study, we used statistical values from the national survey to specify null hypotheses, and did not obtain a complete individual-level dataset from the survey. As a reference we have already employed this method in our previous study (Reference 10).

Comment

Results

1. There was a very low response rate. Only around 10% of cases were included in analysis. This led to study group of 12 and control group of 78.

Response

The response rate was 28.4%, which was not high, but comparable to other studies. This point has been addressed in the previous version. The denominator should not be the initial patients pool we tried to contact, but those whom we succeeded to contact. We added citations.

Amendment

(P20L7) ‘One drawback, inevitable in this type of study, was the limited response rate to the questionnaires, although our response rate at 28.4% was comparable to that in other similar studies. [6,14]
Comment
2. Why is paternity not in table 2 right below Marriage and compared by Fisher exact test?

Response
We added paternity data in the Table 3, along with result of Fischer’s exact test.

Amendment
Table 3
Patients with paternity data.

Comment
3. In table 3, why was ejaculation problems compared with t-test. It should have been a chi-square or Fisher's exact test.

Response
We apologize for the mistake and made the correction in Table 3.

Comment
4. The authors create failure curves for timing of re-operation. This does not seem to be related to their hypothesis.

Response
Mureau et al reported that "An important factor affecting psychosexual adjustment seems to be the age at which surgery was completed (J Urol 154, 1351-1355, 1995). The later the patients underwent surgery, the greater were their inhibitions in seeking sexual contacts and the later they made the first sexual contacts." Figure 3 described the timing of the first reoperation, and along with it, we added the age of the last reoperation, 13.8±8.2 in Study group, and 9.6±5.5 in patients reoperated for non-obstructive cause (p=0.063). In our patients, the age of first Intercourse was not different between Study and the Control group.
Amendments

Results

(P12L8) ‘The age of the last reoperation was 13.8±8.2 y for those who had obstructive complications, and 9.6±5.5 y for those who had non-obstructive complications (p=0.063).’

(P14L4) ‘Although the Study group patients tended to marry older, hesitation before and after the first intercourse was not significantly higher than the Control.’

Discussion

(P18L5) Mureau et al reported that, the later the patients underwent surgery, the greater were their inhibitions in seeking sexual contact and the later they made the first sexual contacts.[18] However, between the patients reoperated for obstructive of non-obstructive cause, the timing of the first and last reoperation was not statistically significant, nor was the age of first intercourse.

References


Comment

5. There were only 5 patients in study group that were married. Of these 5 patients, none had children. Apparently, this leads to a statistically significant finding when compared by log-rank test. However, with only 5 patients making the basis of the main findings of the study, I would not overstate the conclusions.

Response

We appreciate the Reviewer’s comment and critique. Indeed, our finding should be tested in the future study in larger population. Our conclusion is based upon 12 Study group patients, and not only upon 5 married cases. This point has been already addressed in the initial manuscript, on which we made further change.

Amendment

Discussion

(P20L16) ‘Since our data derive from limited number of patients, with 12 Study group patients without offspring, of which only 5 were married, our findings should be further tested by future study by different groups and by ourselves.’
Comment

Discussion

1. I think authors can conclude that overall intercourse, marriage, and marriage with paternity seemed similar to the general population. There is some suggestion that marriage and paternity may be lower in the obstructive group with paternity reaching statistical significance when compared to non-obstructive group. However, very low numbers limit conclusions.

2. Since there were only 12 cases in the study group with only 5 being married, it is really difficult to make any significant conclusions. The authors need to emphasize the small numbers in the discussion and conclusions.

Response

We agree to the Reviewer’s opinion, and we made further modification to emphasize the point in Abstract, Discussion and Conclusions.

Amendment

Abstract

(P3L14) although it should be further tested in the future for larger groups of hypospadias patients.

Discussion

(P20L16) ‘Since our data derive from limited number of patients, with 12 Study group patients without offspring, of which only 5 were married, our findings should be further tested by future study by different groups and by ourselves.’

Conclusions

(P22L1) The findings in this report may suggest that reoperation for urethral obstruction was associated with lower paternity, but because of the limited number of Study patients, it should be further tested by the future studies in larger groups of hypospadias patients.

Comment

3. How is this study really different then their prior study that included 108 patients? I think this is the main limitation of this paper in that it essentially just uses data previously published. They found a similar finding with previous paper. Because this had similar findings using the same data set and patients, I question whether this study needed to be done.
Response

As stated in the introduction section, this is a subanalysis of the previous paper. The topic, kind of analysis, and data presented are different.

Comment

4. Since a staged repair was done on distal and proximal type hypospadias, a re-operation for obstruction could be a sign of hypospadias severity.

Response

The background data on hypospadias type was roughly the same between the groups, as shown in Figure 2 (P=1.0).

Comment

5. Were any of the 12 study group patients wanting to have children? This is important information that is not provided.

Response

We agree to the Reviewer’s comment. We do not have information about patients’ desire for paternity, because these points were not included in the questionnaire. Therefore, we avoided the word ‘infertility’, which should be reserved for those who wish to have child.

(P18L4,L7) fertility -> paternity

Comment

Conclusions

1. They should not start the conclusion with "despite the limitations"

Response

We amended the starting of conclusion.
Amendment

(P22L1) ‘The findings in this report may suggest that reoperation for urethral obstruction was associated with lower paternity, but because of the limited number of Study patients, it should be further tested by the future studies in larger groups of hypospadias patients.’

Comment

2. They can conclude that the group who had reoperation for obstruction seemed to have lower marriage rates than the general population and none of these patients had children which was significantly different than the control group and general population. However, given the low number of patients (12 in study group of which only 5 were married) and lack of information about desire for children it is difficult to state definitively the meaning of these findings.

3. I do not think this report could be used as a reference for other studies given the approach (staged for all patients) and limited number of patients. Overall Very small number of patients.

Response

Conclusion was modified according to the Reviewer’s suggestion.

Amendment

We deleted the description that this report could be used as a reference for other studies.

(P22L1) ‘The findings in this report may suggest that reoperation for urethral obstruction was associated with lower paternity, but because of the limited number of Study patients, it should be further tested by the future studies in larger groups of hypospadias patients.’

Comment

These 90 patients were part of a previous report with 108 patients. Unclear if multiple publications should be made with same patients on same topic.

Response

As stated in the introduction section, this is a subanalysis of the previous paper. The topic, kind of analysis, and data presented are different.