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ORIGINAL ARTICLE

Predictors of subsequent pregnancy in women who underwent laparoscopic cornuostomy or laparoscopic wedge resection for interstitial pregnancy

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Abstract

Background: The ideal surgical procedure for interstitial pregnancy remains undetermined. The aim of this study was to assess whether surgical method is a factor in predicting subsequent pregnancy in women with interstitial pregnancy who underwent laparoscopic cornuostomy or laparoscopic wedge resection.

Methods: Medical records of all women with interstitial pregnancy who underwent laparoscopic cornuostomy or laparoscopic wedge resection between March 2008 and October 2017 in a medical center were reviewed. Cox regression analysis was performed to identify factors predicting subsequent pregnancy.

Results: Forty patients underwent laparoscopic cornuostomy (n = 14) or laparoscopic wedge resection (n = 26) for the treatment of interstitial pregnancy. Twelve women become pregnant during follow-up. Laparoscopic cornuostomy was associated with shorter operation time (coefficient = −19.1 minutes, 95% CI = −36.9 to −1.3 minutes, $p = 0.04$, multivariable analysis) than that of laparoscopic wedge resection. Furthermore, laparoscopic cornuostomy (hazard ratio = 6.3, $p = 0.03$), parity (hazard ratio = 0.18, $p = 0.008$), and preoperative rupture of the cornus (hazard ratio = 13.3, $p = 0.005$) were independent predictors of subsequent pregnancy.

Conclusion: Laparoscopic cornuostomy was associated with a higher probability of subsequent pregnancy and a shorter operation time. Thus, compared with laparoscopic wedge resection, laparoscopic cornuostomy might be a better surgical procedure for women with interstitial pregnancy, particularly for women who wish to become pregnant later. However, because of the retrospective nature and small sample size of this study, some well-defined/designed prospective studies including more patients are needed to verify our results.

Keywords: Cornus; Interstitial pregnancy; Laparoscopy

1. INTRODUCTION

Historically, interstitial pregnancy was treated by local methotrexate injection,[1,2] laparotomic resection, or hysterectomy.[3] Recently, laparoscopic cornuostomy (LC) or laparoscopic wedge resection (LWR) have been used to treat women with interstitial pregnancy.[4–9]

Several studies have reported the use of LC or LWR to manage interstitial pregnancy.[7–9] However, only Lee et al.[9] reported a between-group comparison of LC and LWR and concluded that LC may reduce the surgical time and that the incidence of persistent interstitial pregnancy is the same for both procedures. Nonetheless, to the best of our knowledge, no research has yet investigated which laparoscopic surgical procedure is better for women with interstitial pregnancy, particularly for those who desire a future pregnancy. Thus, the aim of this study was to elucidate whether LC is better than LWR for women with interstitial pregnancy, particularly for those with a desire for a future pregnancy.

2. METHODS

Medical records of all women who underwent LC or LWR for interstitial pregnancy between March 2008 and October 2017 in the Department of Obstetrics & Gynecology of a medical center were reviewed. The Research Ethics Committee of the hospital approved this study. The diagnosis of interstitial pregnancy was defined by the intraoperative identification of the pregnancy as an asymmetric bulge in one of the uterine angles lateral to the insertion of the round ligament.[10]

Baseline characteristics, perioperative data, and follow-up outcomes were compared between the LC and LWR groups. Because the purpose of this study was to elucidate whether LC has a better impact on subsequent pregnancy, women who had a heterotopic pregnancy found during the operation and preserved her intrauterine pregnancy during surgery, who had a documented later pregnancy by artificial reproductive technology, or

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who had ever undergone contralateral salpingectomy or concomitant tubal sterilization were excluded from this study. Only those women with an intact contralateral tube after surgery were included. There were nine surgeons who performed LC or LWR in this study. The choice of operative method (i.e., LC or LWR) was based on each surgeon's preference.

LC was usually performed as follows. Under laparoscopic inspection, the swollen cornus was identified and a linear incision was made to open the cornus, usually after diluted vasopressin local injection. If the cornus ruptured preoperatively, a linear extension was made along the site of rupture. The gestational products were removed using forceps and a suction tube when possible. After the above procedures, oozing was usually found in the implantation site. Active vascular bleeding was usually treated with electrocauterization. Then, the edges of the cornuostomy were approximated with 1-0 Vicryl (Ethicon Inc., Somerville, NJ) or V-Loc (Covidien, Mansfield, MA) sutures, and the surgeon would take care to keep the patency of the interstitial part of the fallopian tube during suturing. After suturing, oozing and related hematoma would be confined within the interstitial space, generating an increase in the intraluminal pressure. The increased intraluminal pressure would be helpful for hemostasis. An abdominal drain was usually placed to monitor any delayed postoperative hemorrhage.

LWR was usually performed as follows. Under laparoscopic inspection, the swollen cornus was identified and resected with monopolar scissors or hooks, usually after diluted vasopressin local injection and occasionally accompanied by salpingectomy, followed by approximation of the remaining myometrial defect with 1-0 Vicryl or V-Loc sutures.

The operation time was calculated from the point of skin incision to the end of the skin wound closure. Blood loss was estimated by calculating the difference between the volumes of aspirated and irrigated fluid. Complications were defined as events requiring active treatment, such as conversion to laparotomy or further laparoscopic surgery for persistent interstitial pregnancy. The surgery-pregnancy interval was calculated from the date of operation to the date of the last menstrual period that documented pregnancy or last follow-up.

The STATA software program (version 11.0; Stata Corp, College Station, TX) was used for statistical analyses. Chi-square test, Wilcoxon rank-sum test, Fisher's exact test or multivariable linear regression analysis were used, as appropriate. Pregnancy probability was estimated using the Kaplan-Meier method. Multivariable backward stepwise Cox regression analysis was performed using all the variables in the univariate analysis.[11] A p value of <0.05 was considered statistically significant.

3. RESULTS

After excluding four cases, forty patients underwent LC (n = 14) or LWR (n = 26) for interstitial pregnancy (Figure 1). The baseline characteristics of the patients are listed in Table 1. Nine gynecologic surgeons performed these surgeries. The decision to perform LC or LWR was based on each surgeon's preference. Among the nine surgeons, five surgeons performed LWR only (n = 22), two surgeons performed LC only (n = 10), and only two surgeons performed both LC and LWR methods (n = 8). Except for body mass index, operation time and blood loss, there were no significant differences in the clinical parameters between the groups. One

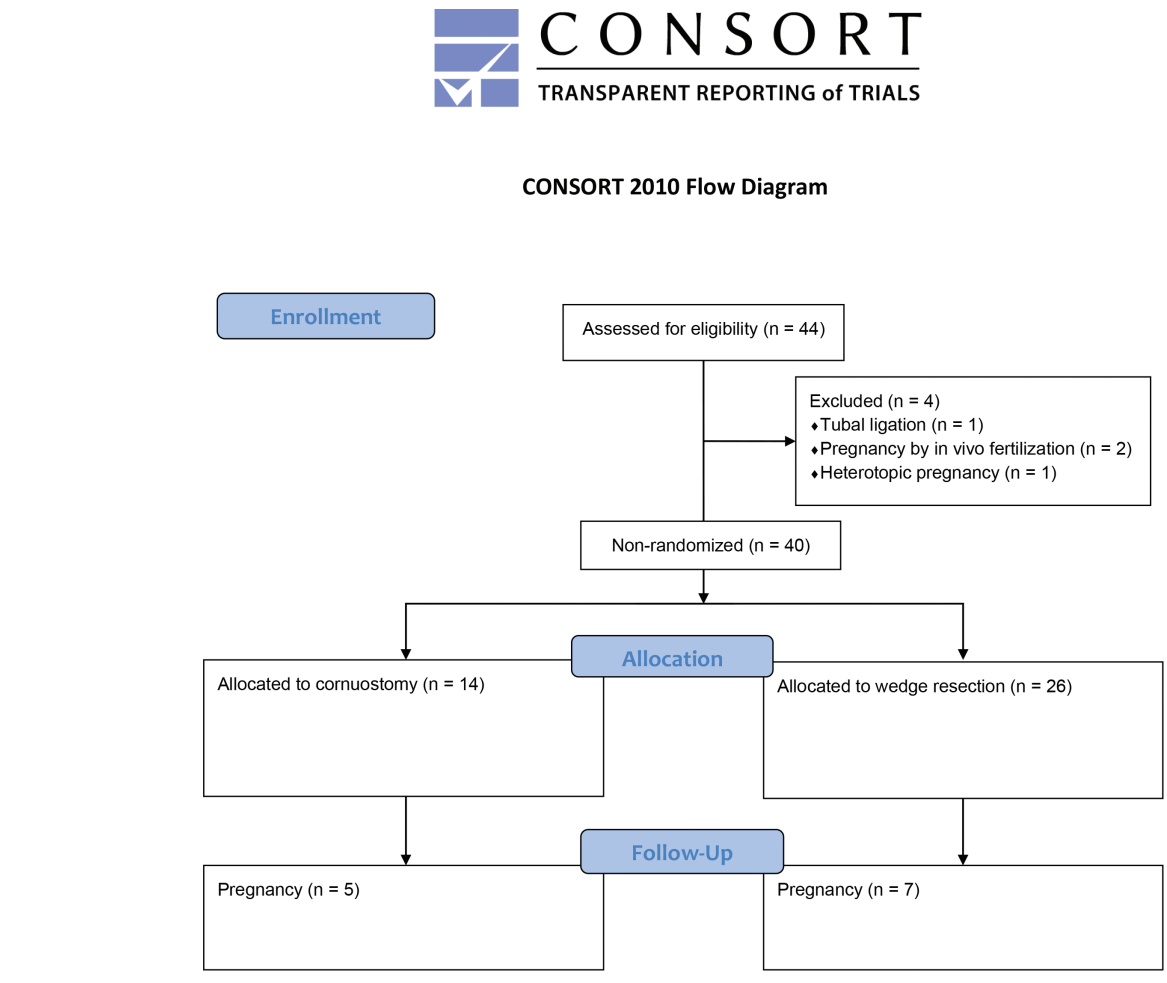

Fig. 1 Flow diagram.

Table 1

Baseline characteristic and clinical outcomes of the laparoscopic wedge resection and cornuostomy groups (n = 40)

Variables	Cornuostomy (n = 14)	Wedge resection (n = 26)	p^a
Age, y	32.8 ± 5.9	33.0 ± 5.5	0.98
Parity	0.7 ± 0.7	1.0 ± 0.9	0.36
Body mass index, kg/m^2	21.6 ± 3.8	23.8 ± 4.0	0.02
Gestational age, wk	7.2 ± 1.1	7.4 ± 2.4	0.54
Gestational mass size, cm	2.3 ± 0.8	3.3 ± 1.5	0.16
Baseline β-hCG, mIU/mL	13472 ± 15396	20222 ± 31830	0.95
Right side of pregnancy	6 (43)	15 (58)	0.37
Preoperative rupture of the cornus	6 (43)	16 (62)	0.26
Operation time, min	64.8 ± 21.7	83.8 ± 28.7	0.009
Blood loss, mL	519 ± 1001	1192 ± 995	0.002
Pregnancy during follow-up	5 (36)	7 (27)	0.72
Adjuvant methotrexate injection	3 (21)	3 (12)	0.65
Median surgery-pregnancy interval, wk	61.9 (5, -)	313.6 (17.6, -)	0.42
Mean follow-up interval, wk	115.9 ± 124.4	102.5 ± 145.7	0.48

Data are expressed as the mean ± SD or number (%).

[a]By Wilcoxon rank-sum test, chi-squared test, Fisher's exact test, or log-rank test.

hCG = human chorionic gonadotropin.

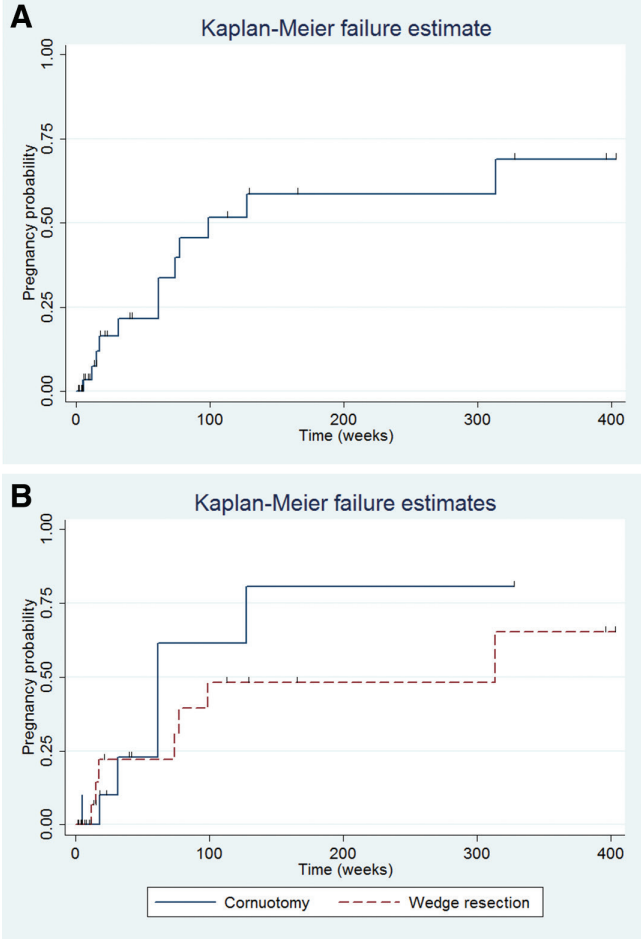

Fig. 2 Subsequent pregnancy probabilities of (A) all women and (B) the laparoscopic cornuostomy and laparoscopic wedge resection groups of women whom underwent surgery for interstitial pregnancy.

patient in the LC group who received an adjuvant methotrexate injection was a case of gestational trophoblastic neoplasia in the cornus that was confirmed after pathologic examination of the surgical specimen. Subsequent pregnancy probability of the whole population and both groups is shown in Figure 2A, B.

Univariate and multivariable backward stepwise Cox proportional hazards regression analyses were performed to predict future pregnancy after surgery for interstitial pregnancy (Tables 2 and 3). Use of the LC method (hazard ratio = 6.3, p = 0.03), parity (hazard ratio = 0.18, p = 0.008), and preoperative rupture of the cornus (hazard ratio = 13.3, p = 0.005) was independent predictors of future pregnancy.

Among eight neonates who were delivered in our hospital, five were delivered by normal spontaneous vaginal delivery and three were delivered by cesarean section. There were no postoperative, perinatal, or obstetrical complications in either group during follow-up.

Operation time was shorter in the LC group than in the LWR group (Table 1). Multivariable backward stepwise regression analysis confirmed that the LC method was the only predictor of operation time (coefficient = –19.1 minutes, 95% CI = –36.9 to –1.3 minutes, p = 0.04).

The amount of blood loss was higher in the LWR group than in the LC group (Table 1). However, multivariable backward stepwise linear regression analysis revealed that preoperative rupture of the cornus was the only predictor (coefficient = 1278 mL, 95% CI = 748–1807 mL, p < 0.001).

4. DISCUSSION

In this study, we found that LC was a significant predictor (hazard ratio = 6.3) of future pregnancy. Watanabe et al.[6] reported that 8 of the 13 women who underwent LC experienced a spontaneous intrauterine pregnancy subsequent to surgery. Ng et al.[8] reported that 18 of 52 (34%) women became pregnant after LC or LWR. Liao et al.[3] reported that 71.4% of the patients who underwent laparotomic wedge resection were able to become pregnant later. However, we did not find any study that has compared the subsequent pregnancy rates between the LC and LWR methods for treating interstitial pregnancy in women who desire subsequent pregnancy. Thus, our result suggests that compared with LWR, LC may be a better procedure for treating patients with interstitial pregnancy who desire a subsequent pregnancy.

In this study, preoperative rupture of the cornus was a predictor of subsequent pregnancy (odds ratio = 13.3). No previous studies have mentioned the relationship between preoperative rupture of the cornus and subsequent pregnancy in women who have undergone surgery for interstitial pregnancy. We speculate that preoperative rupture of the cornus may be associated with more prominent cornual engorgement, and it is easier to obtain adequate cornuostomy wound edges to reconstruct a patent tubal lumen in the interstitial segment after enucleation of the gestational products. In cases of preoperative rupture of the cornus, it should be easier to enter the tubal lumen of the interstitial segment.

Table 2

Comparisons between the pregnancy and nonpregnancy groups and univariate Cox proportional hazards regression analyses for predicting subsequent pregnancy after surgery for interstitial pregnancy (n = 40)

Variables	Pregnancy (n = 12)	Nonpregnancy (n = 28)	p^a	Values	Univariate hazard ratio	p^b
Surgical method						
Cornuostomy (n = 14)	5 (36)	9 (64)	0.56	14 (35)	1.61 (0.50–5.22)	0.42
Wedge resection (n = 26)	7 (27)	19 (73)	…	…	…	…
Age, y	31.6 ± 3.0	33.5 ± 6.3	0.48	33.0 ± 5.5	0.89 (0.80–0.99)	0.04
Parity	0.5 ± 0.7	1.1 ± 0.9	0.04	0.9 ± 0.8	0.42 (0.18–0.95)	0.04
Body mass index, kg/m^2	21.7 ± 4.7	23.6 ± 3.6	0.04	23.0 ± 4.0	1.01 (0.79–1.29)	0.94
Gestational age, wk	7.3 ± 1.8	7.3 ± 2.2	0.63	7.3 ± 2.0	1.06 (0.79–1.41)	0.70
Gestational mass size, cm	2.7 ± 0.9	2.9 ± 1.5	0.79	2.9 ± 1.3	0.63 (0.30–1.32)	0.22
Baseline β-hCG, mIU/mL	15771 ± 16805	18535 ± 30320	0.69	17735 ± 26906	1.000 (1.000–1.000)	0.39
Right side of pregnancy	7 (33)	14 (67)	0.63	21 (53)	1.26 (0.40–4.00)	0.69
Preoperative rupture of cornus	7 (32)	15 (68)	0.78	22 (55)	2.29 (0.72–7.29)	0.16
Operation time, min	73.3 ± 22.8	78.8 ± 29.9	0.71	77.2 ± 27.7	1.004 (0.979–1.029)	0.78
Blood loss, mL	1151 ± 1315	874 ± 908	0.76	957 ± 1037	1.001 (1.000–1.001)	0.03

Values are expressed as the mean ± SD, number (%), or hazard ratio (95% CI).

[a]By chi-squared test or Wilcoxon rank-sum test.

[b]Cox proportional hazards regression analyses.

hCG = human chorionic gonadotropin.

Table 3

Multivariable backward stepwise Cox proportional hazards regression analyses for predicting subsequent pregnancy after surgery for interstitial pregnancy (n = 40)

Variables	Multivariable hazard ratio	p^a
Cornuostomy method	6.3 (1.2–33.9)	0.03
Parity	0.18 (0.05–0.63)	0.008
Preoperative rupture of the cornus	13.3 (2.2–81.0)	0.005

Values are expressed as the hazard ratio (95% CI).

[a]Multivariable backward stepwise Cox proportional hazards regression analyses was performed using all variables in the univariate analysis of Table 2. Herein, we do not show the data without statistical significance.

Parity was another negative predictor of subsequent pregnancy (odds ratio = 0.18). In the era of low birth rates, it is not difficult to imagine that increased parity is associated with a low rate of subsequent pregnancy. In addition, among the nine surgeons in this study, five surgeons performed LWR only (n = 22), two surgeons performed LC only (n = 10), and only two surgeons performed both LC and LWR methods (n = 8). Thus, parity is less likely to be a major consideration for LWR in this study.

LWR was reported to be particularly useful for interstitial pregnancy >4 cm in diameter.[12,13] However, we did not use the above criteria for the selection of surgical method for interstitial pregnancy. In this study, the LC group was associated with a shorter operation time (coefficient = −19.1 minutes, 95% CI = −36.9 to −1.3 minutes, p = 0.04) than that of the LWR group. Lee et al.[9] also reported that the operation time of LC was significantly shorter than that of LWR. The above findings suggest that LC might be a better choice for interstitial pregnancy.

In our study, the LC method and preoperative rupture of the cornus were statistically nonsignificant in the univariate analysis (Table 2; Figure 2B) but significant in the multivariable analysis (Table 3). Some scenarios, such as the effect of an unbalanced sample size, the influence of missing data, an extremely large within-group variation, and the presence of interactions, may result in some variables being nonsignificant in the univariate analysis but significant in the multivariable analysis,[14] as was observed in our study. In Figure 2B, the curves did not reach statistical significance (p = 0.42, log-rank test, Table 1). However, multivariable analysis showed that LC was a predictor of future pregnancy (p = 0.03, Table 3). The above discrepancy in statistical significance between log-rank test and multivariable analysis might be related to unbalanced sample size, as was observed by the study of Lo et al.[14]

Because our aim was to elucidate whether LC or LWR can affect subsequent pregnancy, thus we only include women with intact contralateral tubes. In women without intact contralateral tubes, LWR would make the patients infertile and might bias our result.

This study has some limitations. This retrospective study was not a randomized trial and had a limited sample size. However, we used multivariable Cox regression analysis to improve our reliability. Owing to the retrospective nature of this study, we did not identify women who had no plan for further conception and we did not exclude the above population from this study. In addition, the patency of contralateral tube was not routinely checked during surgery and this might be one of the confounding factors.

In conclusion, LC was associated with higher subsequent pregnancy probability and shorter operation time than that of LWR. Thus, LC might be a better surgical procedure for women with interstitial pregnancy, particularly for women who wish to become pregnant later. However, because of the retrospective nature and small sample size of this study, some well-defined/designed prospective studies including more patients are needed to verify the results.

REFERENCES

1. Benifla JL, Fernandez H, Sebban E, Darai E, Frydman R, Madelenat P. Alternative to surgery of treatment of unruptured interstitial pregnancy: 15 cases of medical treatment. *Eur J Obstet Gynecol Reprod Biol* 1996;**70**:151–6.
2. Leggieri C, Guasina F, Casadio P, Arena A, Pilu G, Seracchioli R. Hysteroscopic methotrexate injection under ultrasonographic guidance for interstitial pregnancy. *J Minim Invasive Gynecol* 2016;**23**:1195–9.
3. Liao CY, Tse J, Sung SY, Chen SH, Tsui WH. Cornual wedge resection for interstitial pregnancy and postoperative outcome. *Aust N Z J Obstet Gynaecol* 2017;**57**:342–5.
4. Manea C, Pavlidou E, Urias AA, Bouquet de la Jolinière J, Dubuisson JB, Feki A. Laparoscopic management of interstitial pregnancy and fertility outcomes after ipsilateral salpingectomy - three case reports. *Front Surg* 2014;**1**:34.
5. Soriano D, Vicus D, Mashiach R, Schiff E, Seidman D, Goldenberg M. Laparoscopic treatment of cornual pregnancy: a series of 20 consecutive cases. *Fertil Steril* 2008;**90**:839–43.
6. Watanabe T, Watanabe Z, Watanabe T, Fujimoto K, Sasaki E. Laparoscopic cornuotomy for interstitial pregnancy and postoperative course. *J Obstet Gynaecol Res* 2014;**40**:1983–8.

7. MacRae R, Olowu O, Rizzuto MI, Odejinmi F. Diagnosis and laparoscopic management of 11 consecutive cases of cornual ectopic pregnancy. *Arch Gynecol Obstet* 2009;**280**:59–64.
8. Ng S, Hamontri S, Chua I, Chern B, Siow A. Laparoscopic management of 53 cases of cornual ectopic pregnancy. *Fertil Steril* 2009;**92**:448–52.
9. Lee MH, Im SY, Kim MK, Shin SY, Park WI. The comparison of laparoscopic cornual resection and cornuotomy for interstitial pregnancy. *J Minim Invasive Gynecol* 2017;**24**:397–401.
10. Nirgianakis K, Papadia A, Grandi G, McKinnon B, Bolla D, Mueller MD. Laparoscopic management of ectopic pregnancies: a comparison between interstitial and "more distal" tubal pregnancies. *Arch Gynecol Obstet* 2017;**295**:95–101.
11. Altman DG. *Practical statistics for medical research*. London: Chapman & Hall; 1991, p. 325–364.
12. Tulandi T, Vilos G, Gomel V. Laparoscopic treatment of interstitial pregnancy. *Obstet Gynecol* 1995;**85**:465–7.
13. Moawad NS, Mahajan ST, Moniz MH, Taylor SE, Hurd WW. Current diagnosis and treatment of interstitial pregnancy. *Am J Obstet Gynecol* 2010;**202**:15–29.
14. Lo SK, Li IT, Tsou TS, See L. Non-significant in univariate but significant in multivariate analysis: a discussion with examples. *Changgeng Yi Xue Za Zhi* 1995;**18**:95–101. [Chinese]