Fertility and ileal pouch-anal anastomosis

I read with interest the meta-analysis of infertility post ileal pouch-anal anastomosis (IPAA) published by Waljee and colleagues in the November issue.¹ The article consolidates the increasing evidence that this procedure is associated with a significant decrease in female fertility.

Having recently reviewed the studies in their analysis, however, I was surprised the authors had included data from the following two trials; the first by Wikland *et al*² assessed 41 patients treated exclusively with conventional proctocolectomy with ileostomy rather than IPAA; the other, by Hudson *et al*,³ included 20 patients treated with surgery of which only two had IPAA, while the remainder were treated with either proctocolectomy and ileostomy or colectomy and ileorectal anastomosis. Waljee *et al* deliberately and correctly excluded another similar study⁴ for the very reason that it investigated proctocolectomy with ileostomy, not IPAA. IPAA may have a different effect on fertility and sexual function to proctocolectomy alone, as different pelvic anatomic changes will be present. In particular, the presence of the neo-rectum may prevent caudal sliding of the adnexae and posterior displacement of the vagina.² Wikland's data showed an increase in infertility from 29.6% before surgery to 57.2% post-proctocolectomy and ileostomy and Hudson's results also demonstrated a negative effect of surgery on fertility. However I doubt the inclusion of these small studies has significantly altered the outcome of the meta-analysis.

Wikland's study does demonstrate that fertility is also adversely affected by proctocolectomy and ileostomy. This suggests it may be the extensive pelvic dissection involved in proctocolectomy rather than the IPAA itself which is responsible for the decrease in fertility. Further support is added to this hypothesis by a recent study of patients with familial adenomatous polyposis comparing IPAA with colectomy and ileorectal anastomosis, demonstrating that the latter procedure, in avoiding pelvic dissection, preserves female fertility.⁵ While rectal preservation is seldom an option in ulcerative colitis patients, this evidence does mandate the careful consideration of fertility in the choice and timing of operation for ulcerative colitis.

Correspondence to: Mr Timothy W Eglinton, FRACS, Senior Clinical Fellow Coloproctology, Cambridge Colorectal Unit, Box 201, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Rd, Cambridge CB2 2QQ, United Kingdom; timeglinton015@aol.com

Competing interests: None.

References

- Waljee A, Waljee J, Morris A, *et al*. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006;55:1575-1580.
- Wikland M, Jansson I, Asztely M, *et al*. Gynaecological problems related to anatomical changes after conventional proctocolectomy and ileostomy. *Int J Colorectal Dis* 1990;5:49-52.
- Hudson M, Flett G, Sinclair T, *et al*. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997;58:229-37.
- Scaglia M, Bronsino E, Canino V, *et al*. The impact of conventional proctocolectomy on sexual function. *Minerva Chir* 1993;48:903-10.

5 Olsen K, Juul S, Bulow S, *et al*. Female fecundity before and after operation for familial adenomatous polyposis. *British Journal of Surgery* 2003;90:227-231.

Authors' response

We thank you for your interest in our study. Although, as Eglinton noted, the article by Wikland *et al*¹, does not fit our stated inclusion criteria, we found that its exclusion has little impact on our results and further supported our conclusions. Most importantly, after excluding the study by Wikland, the finding that patients with ileal pouch anal anastomosis have a threefold increased relative risk (RR) of infertility is unchanged. However, the estimates of RR of infertility did increase slightly. For the fixed-effects model in fig 3A, the corrected RR was 3.31 (95% CI 2.47 to 4.44). For the random effects model in fig 3B, the corrected RR was 3.15 (95% CI 2.26 to 4.39).

We were intrigued by Eglinton's hypothesis that the studies of Wikland² and Scaglia³ demonstrate that it is the pelvic dissection needed for proctocolectomy, and not necessarily pouch construction, that leads to infertility. The data from these two studies are suggestive, but we believe that they do not offer sufficient statistical power to conclude that infertility rates are equivalent in ileostomy versus ileal pouch anal anastomosis. Further studies are needed to better understand the aetiology of infertility in patients with ulcerative colitis after colectomy.

Akbar K Waljee

Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

Jennifer F Waljee

Department of Surgery, University of Michigan, Ann Arbor, Michigan, USA

Arden M Morris

Division of Colorectal Surgery, University of Michigan, Department of Surgery, Ann Arbor, Michigan, USA

Peter D R Higgins

Division of Gastroenterology, University of Michigan, Department of Internal Medicine, Ann Arbor, Michigan, USA

Correspondence to: Dr P D R Higgins, Division of Gastroenterology, University of Michigan, 6520 MSRB I, Box 0682, 1150 West Medical Center Drive, Ann Arbor, MI 48109, USA; phiggins@umich.edu

Competing Interests: None declared.

References

- Wikland M, Jansson I, Asztely M, *et al*. Gynaecological problems related to anatomical changes after conventional proctocolectomy and ileostomy. *Int J Colorectal Dis* 1990;5:49-52.
- Scaglia M, Bronsino E, Cannini U, *et al*. The impact of conventional proctocolectomy on sexual function. *Minerva Chir* 1993;48:903-10.

Transplantation for alcoholic liver disease

Alcohol relapse can negatively influence the outcome after liver transplantation and factors that could be associated with the recurrence of harmful alcohol consumption after liver transplantation are still poorly described. We recently presented the results of a study¹ dealing with this issue in a large cohort of patients transplanted for alcoholic liver disease. Our findings are in accordance with the

observations by O'Grady in a recent leading article in *Gut*,² but expand to some novel aspects, which we would like to focus on.

In all, 387 consecutive patients, transplanted for alcoholic cirrhosis in Geneva and Lyon, were followed up for a mean duration of 61.2 months. Relapse of harmful alcohol consumption after liver transplantation was observed in 11.9%. In univariate analysis, return to harmful alcohol drinking—defined as a daily consumption >40 g associated with physical or mental damage related to alcohol,³ was significantly associated with age >50 years ($p=0.04$), duration of abstinence <6 months ($p=0.02$), psychiatric comorbidities ($p<0.001$), absence of a life partner ($p<0.05$) and an increased high-risk alcohol relapse⁴ (HRAR) score ($p<0.001$). Alcohol relapse was 6.6% in patients without psychiatric comorbidities and up to 69.6% in patients with psychiatric comorbidities ($p<0.001$). Multivariate logistic regression disclosed that duration of abstinence <6 months (odds ratio (OR) 3.3, 95% confidence interval (CI) 1.2 to 9.3, $p=0.02$), psychiatric comorbidities (OR 7.8, 95% CI 3.1 to 20, $p<0.001$) and high-risk alcohol relapse score >3 (OR 10.7, 95% CI 3.8 to 30, $p<0.001$) were independent factors of relapse. In patients presenting none of these factors, alcohol relapse was 4.8%, whereas the presence of 1, 2 or 3 factors together was associated with relapse in 17.8%, 63.6% and 100% of the patients, respectively.

Although the results of this study support the validity of the 6-month abstinence rule, they relegate it behind two other major factors, which are susceptible of predicting relapse. As a consequence, we only partially share the author's position for the endorsement of this rule, as it appears to be an insufficient element of decision, when considered as the sine qua non condition for a favourable assessment. Additionally, we believe that obtaining accurate information on the general population about the limits of this rule would be preferable to a rigid requirement based on debated evidence. The availability of additional parameters, as suggested in our study, to predict return to heavy drinking after liver transplantation will probably help us to use organs to the best of their potential. The data of the present study, although waiting to be independently validated, may provide novel insights into the criteria for the selection of patients with alcoholic liver disease, who are candidates for liver transplantation, and may facilitate our future decisions.

Andrea De Gottardi

Division d'Hépatogastroentérologie, Hôpitaux Universitaires, Genève, Switzerland

Jérôme Dumortier

Fédération des Spécialités Digestives, Hôpital Edouard Herriot, Lyon, France

Correspondence to: Dr Andrea De Gottardi, Division d'Hépatogastroentérologie, Hôpitaux Universitaires, 1205 Genève, Switzerland; andrea.degottardi@hcuge.ch

doi: 10.1136/gut.2006.115022

Published Online First 4 December 2006

Competing interests: None.

References

- De Gottardi A, Spahr L, Gelez P, *et al*. Is alcohol relapse after liver transplantation predictable?

Results in 387 patients over 15 years [abstract 1428]. *Am J Transplant* 2006;6:546.

- 2 O'Grady JG. Liver transplantation alcohol related liver disease: (deliberately) stirring a hornet's nest! *Gut* 2006;55:1529–31.
- 3 ICD Version 2006: World Health Organization 2006.
- 4 Yates WR, Booth BM, Reed DA, et al. Descriptive and predictive validity of a high-risk alcoholism relapse model. *J Stud Alcohol* 1993;54:645–51.

Role of *RET* and *PHOX2B* gene polymorphisms in risk of Hirschsprung's disease in Chinese population

Hirschsprung's disease (OMIM 142623) is a complex congenital disorder characterised by the absence of ganglion cells of the plexus myentericus and plexus submucosus in the variable lengths of the digestive tract.^{1,2} Aganglionosis is attributed to a defect of the enteric nervous system, in which ganglion cells fail to innervate the lower gastrointestinal tract during embryonic development, resulting in failure to pass meconium, chronic severe constipation and colonic distention in the neonatal period.³ The receptor tyrosine kinase gene *RET*, which is expressed in neural crest cells during enteric neurogenesis and is required for normal development of the enteric nervous system, is the major susceptibility gene for Hirschsprung's disease.⁴ There is growing evidence indicating that functional single nucleotide polymorphisms (SNPs) of *RET* could act as low susceptibility factors for Hirschsprung's disease.^{5,6} In addition, *PHOX2B* encodes a transcription factor that is involved in the development of the noradrenergic nervous system and that plays an important role in the regulation of *RET* transcription.^{7,8} Our previous data showed that genotypes comprising allele A of the IVS2+100 A>G SNP of *PHOX2B* were associated with an increased risk of Hirschsprung's disease.⁹ In view of the role of *RET* and *PHOX2B* in the development of the enteric nervous system, we hypothesised that *RET* and *PHOX2B* polymorphisms are likely to interact and have a joint effect in conferring susceptibility to Hirschsprung's disease.

This case-control study consisted of 256 ethnic Chinese patients histologically diagnosed with sporadic Hirschsprung's disease, including 13 patients with total colonic aganglionosis, 28 with long-segment aganglionosis and 215 with short-segment aganglionosis. Controls were 242 unselected, unrelated, ethnic Chinese subjects. At recruitment, informed consent was obtained from each subject. This study was approved by the institutional review board of the University of Hong Kong. Genotypes for *RET* promoter polymorphisms (5G>A and 1A>C) and *PHOX2B* were analysed using polymerase chain reaction and direct sequencing, as described previously.^{6,9}

We observed an increased risk of Hirschsprung's disease in homozygous genotypes of the disease-associated *RET* alleles 5AA or ICC when compared with 5GA and 5GG (OR = 7.78, 95% CI 5.21 to 11.70), or 1AC and 1AA (OR = 6.08, 95% CI 4.01 to 9.12) genotypes. The same risk was seen with the *PHOX2B* IVS2+100 AA genotype compared with the GG or GA genotypes (OR = 1.75, 95% CI 1.17 to 2.58). We then investigated the potential interaction between the *RET* and *PHOX2B* genotypes in the risk of Hirschsprung's disease using the additive

Table 1 Risk of Hirschsprung's disease associated with *RET* genotypes combined with *PHOX2B* genotypes

Genotype		Patients (n=256)	Controls (n=242)	
<i>RET</i> -5G/A	<i>PHOX2B</i>	n (%)	n (%)	OR* (95% CI)
GG + GA	GG + GA	19 (7.4)	65 (26.9)	1.00
GG + GA	AA	57 (22.2)	122 (50.4)	1.56 (0.82–2.75)
AA	GG + GA	36 (14.1)	15 (6.2)	7.98 (3.64–17.60)
AA	AA	144 (56.3)	40 (16.5)	11.72 (6.35–21.55)

* ORs and 95% CIs were calculated by unconditional logistic regression adjusted for gender.

interaction models (table 1).¹⁰ Since the 5 and 1 *RET* SNPs were in almost complete linkage disequilibrium in our population ($D' = 0.986$, $p < 0.001$), only the former was selected for further analysis. Among subjects carrying at least one *RET* 5G allele or at least one *PHOX2B* G allele, the OR for Hirschsprung's disease was 1.56 (95% CI 0.82 to 2.75) or 7.98 (95% CI 3.64 to 17.60). The OR increased, however, to 11.72 (95% CI 6.35 to 21.55) among subjects carrying both the *RET* 5AA and *PHOX2B* AA genotypes ($p < 0.001$, test for homogeneity). The OR value of 11.72 is larger than the values of the *RET* 5AA and the *PHOX2B* AA genotypes independently ($7.78 + 1.75 - 1 = 8.53$), which indicates a more than additive interaction between the *RET* and the *PHOX2B* SNPs on risk of developing Hirschsprung's disease according to the statistical model.¹⁰

To our knowledge, this is the first study to demonstrate that the interaction between *RET* and *PHOX2B* polymorphisms has a substantial impact on risk of Hirschsprung's disease. This recognised multifactorial genetic disorder requires the interaction of several unlinked genes to produce the phenotype. Both *RET* and *PHOX2B* have important roles in the development of the enteric nervous system and *PHOX2B* is involved in the transcriptional regulation of *RET* in cell lines originated from neural crest. It is therefore biologically plausible that a joint effect of *RET* and *PHOX2B* SNPs affect the risk of Hirschsprung's disease. However, the essential mechanisms behind our finding need to be investigated.

Acknowledgements

We extend our gratitude to all subjects who participated in the study. This work was supported by the research grant HKU 7392/04M from the Hong Kong Research Grants Council to Maria-Mercè Garcia-Barceló.

Xiaoping Miao*, Maria-Mercè Garcia-Barceló*, Man-ting So, Thomas Yuk-yu Leon, Danny Kachun Lau, Ting-Ting Liu, Edwin Kin-Wai Chan, Lawrence Chuen-Leung Lan, Kenneth Kak-yuen Wong, Vincent Chi-hang Lui, Paul Kwong-hang Tam

Department of Surgery, Genome Research Center, The University of Hong Kong, Pok Fu Lam, Hong Kong SAR, China

Maria-Mercè Garcia-Barceló, Paul Kwong-hang Tam

Genome Research Center, The University of Hong Kong, Pok Fu Lam, Hong Kong SAR, China

Correspondence to: Prof. Paul K H Tam, Division of Paediatric Surgery, Department of Surgery, Queen Mary Hospital, Deputy Director of the Genome Research Centre, University of Hong Kong Medical Centre, Hong Kong, China; paultam@hkuc.hku.hk

doi: 10.1136/gut.2006.116145

*Both authors contributed equally to this work.

Competing interests: None declared.

References

- 1 Amiel J, Lyonnet S. Hirschsprung disease, associated syndromes, and genetics: a review. *J Med Genet* 2001;38:729–39.
- 2 Brooks AS, Oostra BA, Hofstra RM. Studying the genetics of Hirschsprung's disease: unraveling an oligogenic disorder. *Clin Genet* 2005;67:6–14.
- 3 Iwashita T, Kruger GM, Pardoll R, et al. Hirschsprung disease is linked to defects in neural crest stem cell function. *Science* 2003;301:972–6.
- 4 Angrist M, Kauffman E, Slaugenhaupt SA, et al. A gene for Hirschsprung disease (megacolon) in the pericentromeric region of human chromosome 10. *Nat Genet* 1993;4:351–6.
- 5 Garcia-Barceló MM, Sham MH, Lui VC, et al. Chinese patients with sporadic Hirschsprung's disease are predominantly represented by a single *RET* haplotype. *J Med Genet* 2003;40:e122.
- 6 Garcia-Barceló M, Ganster RW, Lui VC, et al. TTF-1 and *RET* promoter SNPs: regulation of *RET* transcription in Hirschsprung's disease. *Hum Mol Genet* 2005;14:191–204.
- 7 Pattyn A, Morin X, Cremer H, et al. The homeobox gene *Phox2b* is essential for the development of autonomic neural crest derivatives. *Nature* 1999;399:366–70.
- 8 Baccetti T, Borghini S, Ravazzolo R, et al. An in vitro approach to test the possible role of candidate factors in the transcriptional regulation of the *RET* proto-oncogene. *Gene Expr* 2005;12:137–49.
- 9 Garcia-Barceló M, Sham MH, Lui VC, et al. Association study of *PHOX2B* as a candidate gene for Hirschsprung's disease. *Gut* 2003;52:563–7.
- 10 Kleinbaum DG. Epidemiologic methods: the "art" in the state of the art. *J Clin Epidemiol* 2002;55:1196–200.

The incidence and risks of liver biopsy in non-cirrhotic patients: An evaluation of 3806 biopsies

Liver biopsy plays a crucial role in the diagnosis and management of liver diseases. For the past decade, this invasive procedure has become a safe one with the prevailing application of an ultrasound-guided method, the use of thinner gauge needles and improved operational techniques. Over the past years, the debatable issue of liver biopsy has mainly focused on the safety and suitability of a shorter observation time with respect to cost savings.^{1–3} Referring to this issue, Beddy et al even shortened their observation time to 1 hour and indicated that only one haemorrhagic complication occurred within one hour amongst 500 liver biopsy occasions. There were no recorded delayed complications or deaths at follow up.⁴

Generally, we agree with the conclusion that outpatient liver biopsy is safe when done in a