1 Fernandez-Fernandezovani FJ: Hereditary haemorrhagic telangiectasia: from symptomatic management to pathogenesis based treatment. *Eur J Hum Genet* 2009, doi:10.1038/ejhg.2009.188 (this issue).
2 Govani FS, Shovlin CL: Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet* 2009; **17**: 860–871.
3 Park SO, Wankhede M, Lee YJ *et al*: Real-time imaging of *de novo* arteriovenous malformation in a mouse model of hereditary hemorrhagic telangiectasia. *J Clin Invest* 1 October 2009. pii: 39482. doi: 10.1172/JCI39482 [Epub ahead of print].
4 Mitchell A, Adams LA, MacQuillan G, Tibballs J, van den Driesen R, Delriviere L: Bevacizumab reverses need for liver transplantation in hereditary hemorrhagic telangiectasia. *Liver Transplant* 2008; **14**: 210–213.
5 Bose P, Holter JL, Selby GB: Bevacizumab in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2009; **360**: 2143–2144.
6 Simonds J, Miller F, Mandel J, Davidson TM: The effect of bevacizumab (Avastin) treatment on epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2009; **119**: 988–992.
7 Massoud O, Youssef W, Mullen K: Resolution of hereditary hemorrhagic telangiectasia and anemia with prolonged [alpha]-interferon therapy for chronic hepatitis C. *J Clin Gastroenterol* 2004; **38**: 377–379.
8 Wheatley-Price P, Shovlin C, Chao D: Interferon for metastatic renal cell cancer causing regression of hereditary hemorrhagic telangiectasia. *J Clin Gastroenterol* 2005; **39**: 344–345.
9 Kurstin R: Using thalidomide in a patient with epithelioid leiomyosarcoma and Osler-Weber-Rendu disease. *Oncology (Williston Park)* 2002; **16**: 21–24.
10 Pérez-Encinas M, Rabuñal Martínez MJ, Bello López JL: Is thalidomide effective for the treatment of gastrointestinal bleeding in hereditary hemorrhagic telangiectasia? *Haematologica* 2002; **87**: ELT34.
11 de Gussem EM, Snijder RJ, Disch FJ, Zanen P, Westermann CJ, Mager JJ: The effect of N-acetylcysteine on epistaxis and quality of life in patients with HHT: a pilot study. *Rhinology* 2009; **47**: 85–88.
12 Yaniv E, Preis M, Hadar T, Shvero J, Haddad M: Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. *Laryngoscope* 2009; **119**: 284–288.

Hereditary haemorrhagic telangiectasia and genetic thrombophilia

European Journal of Human Genetics (2010) **18,** 405; doi:10.1038/ejhg.2009.204; published online 11 November 2009

Govani and Shovlin[1] recently described the clinical and diagnostic implications of hereditary haemorrhagic telangiectasia (HHT). The authors[1] do not seem to be paying attention to the possible presence of genetic thrombophilic risk in HHT patients in relation to pharmacological treatment. Recently, we published[2] a case of HHT and genetic thrombophilia with pharmacological complications attributed to the coexistence of both genetic conditions.

In the review paper, the authors[1] also highlight the risks of life-threatening maternal complications in pregnant HHT women. It is well known that up to 65% of vascular gestational abnormalities can be accounted for by genetic thrombophilias.[3] Therefore, it is possible that women with HHT may have recurrent pregnancy loss or other pregnancy complications because of to thrombophilic gene mutations. In the presence of thrombophilic risk, therapy with acetylsalicylic acid and low molecular heparin is recommended, but this may increase the risk of haemorrhages in the presence of HHT. To our knowledge, there are no data on the incidence of pregnancy complications, such as fetal loss or venous thrombosis, in HHT patients. As reported by Undas *et al.*,[4] in the absence of life-threatening haemorrhages and detectable vascular malformations, oral anticoagulation could be considered with strictly haematological and clinical follow-up. An associated thrombotic tendency may confer a survival advantage for HHT patients by decreasing the severity of their bleeding problems.[5]

We suggest that for the clinical management of these patients, genetic tests and counselling for inherited thrombophilia may be useful to prevent vascular and pregnancy complications and that more appropriate pharmacological treatment in consideration of the possible presence of both genetic conditions is used.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

S Bianca[1], N Cutuli[2], M Bianca[3], B Barrano[1], A Cataliotti[1], C Barone[1], L Indaco[1] and G Milana[2]
[1]*Centro di Consulenza Genetica e di Teratologia della Riproduzione, Laboratorio di Citogenetica, Dipartimento Materno Infantile, PO Garibaldi-Nesima, Catania, Italy;*
[2]*Laboratorio di Genetica Molecolare Umana, Az. Osp. Univ. Policlinico, Catania, Italy;*
[3]*UOC Neurologia - PO Garibaldi-Nesima, Catania, Italy*
E-mail: sebastiano.bianca@tiscali.it

1 Govani FS, Shovlin CL: Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet* 2009; **17**: 860–871.
2 Bianca S, Cutuli N, Bianca M *et al*: Clinical management of Rendu-Osler-Weber syndrome and genetic thrombophilia. *Blood Coagul Fibrinol* 2009 (in press).
3 Kupferminc MJ, Eldor A, Steinman N *et al*: Increased frequency of genetic thrombophilias in women with complications of pregnancy. *N Engl J Med* 1999; **340**: 9–13.
4 Undas A, Bazan-Socha S, Swadzba J, Musial J: Hereditary hemorrhagic telangiectasia, factor V leiden and antiphospholipid syndrome: a case report. *Blood Coagul Fibrinol* 2002; **13**: 53–56.
5 Wechalekar A, Parapia L: Hereditary haemorrhagic telangiectasia with protein S deficiency in a family: a case report. *Eur J Haematol* 2000; **64**: 59–60.

Reply to Bianca *et al*

European Journal of Human Genetics (2010) **18,** 405–406; doi:10.1038/ejhg.2009.205; published online 11 November 2009

We thank Bianca *et al*[1] for their interesting comments and hereditary haemorrhagic telangiectasia (HHT) case reports. Within our structured 2009 *EJHG* review,[2] we did not have space to discuss in detail all of the implications of the cited studies, including, of relevance here, our large thrombosis[3] and pregnancy[4] HHT data series (*EJHG* references 9 and 48).

Concern regarding thrombophilic risk in HHT patients in relation to pharmacological treatment was one of the main conclusions of our cited (*EJHG* reference 9) series of 309 HHT-affected individuals.[3]

When reviewing this manuscript, we stated that the disease spectrum in HHT now encompasses a prothrombotic state, and in Table 2, recommended ensuring that the patient is not prothrombotic before giving oestrogen–progesterone treatment or antifibrinolytic systemic treatment.[2] This referred to the complex clinical management issues regarding blood loss limitation in HHT, when therapeutic manipulation of coagulation and fibrinolytic pathways may be used. As we stated in the final paragraphs, 'routine measurement of FVIII, FV Leiden, and other thrombophilic markers in HHT patient assessments may assist individualised risk-benefit considerations'.[3] We thank Dr Bianca and colleagues for allowing these important considerations to be highlighted again.

Dr Bianca and colleagues also speculate on a possible association between genetic thrombophilias and vascular gestation abnormalities, stating 'To our knowledge there are no data on the incidence of pregnancy complications, like fetal loss or venous thrombosis, in HHT patients'. These data are in fact available, and were presented in our cited (*EJHG* reference 58) series of 484 HHT pregnancies published in *BJOG*.[4] As stated in that manuscript's introduction,[4] there was no evidence for increased fetal loss in HHT pregnancies in the two separate studies that analysed the outcomes, first in 40 women with HHT compared with 80 matched controls,[5] and second, in 161 HHT pregnancies.[6] Pregnancy-related thromboembolic events would be expected in a proportion of women, in keeping with general gestational pathophysiology, and we are aware of an unreported HHT maternal death in pregnancy that occurred because of pulmonary embolism. However, the most frequent life-threatening risks of pregnancy in the series of 484 HHT-affected women were related to haemorrhage from pulmonary and cerebral arteriovenous malformations.[4] The overall maternal death rate was 1.0% (95% confidence interval 0.13–1.9%).[4]

Dr Bianca and colleagues suggest that to prevent vascular and pregnancy complications in patients with HHT and proven thrombophilia, 'more appropriate pharmacological treatment' should be considered. In our experience, even in the setting of HHT and known Factor V Leiden and/or PT20210A heterozygosity, such prophylactic considerations are highly challenging for patients and clinicians, and are not to be undertaken lightly.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Claire L Shovlin[1,2] and Fatima S Govani[2]
[1]HHTIC London, Respiratory Medicine, Hammersmith Hospital, Imperial College Healthcare Trust, London;
[2]NHLI Cardiovascular Sciences, Imperial College London, Hammersmith Hospital, London, UK
E-mail: c.shovlin@imperial.ac.uk

1 Bianca S, Cutuli N, Bianca M *et al*: Hereditary haemorrhagic telangiectasia and genetic thrombophilia. *Eur J Hum Genet* 2009, E-pub ahead of print, Novermber 2009, doi: 10.1038/ejhg.2009.204.
2 Govani FS, Shovlin CL: Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet* 2009; **17**: 860–871.
3 Shovlin CL, Sulaiman NL, Govani FS, Jackson JE, Begbie ME: Elevated factor VIII in hereditary haemorrhagic telangiectasia (HHT): association with venous thromboembolism. *Thromb Haemost* 2007; **98**: 1031–1039.
4 Shovlin CL, Sodhi V, McCarthy A, Lasjaunias P, Jackson JE, Sheppard MN: Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): suggested approach for obstetric services. *BJOG* 2008; **115**: 1108–1115.
5 Goodman RM, Gresham GE, Roberts PL: Outcome of pregnancy in patients with hereditary hemorrhagic telangiectasia. *Fertil Steril* 1967; **18**: 272–277.
6 Shovlin CL, Winstock AR, Peters AM, Jackson JE, Hughes JMB: Medical complications of pregnancy in hereditary haemorrhagic telangiectasia. *Q J Med* 1995; **88**: 879–887.