termed early clamping. Anecdotally, there has been no evidence of significant harm to these infants. Scientifically, the changes that have been noted are of arguable long-term medical consequence. If it were clearly detrimental to the health of the child to perform clamping in one fashion or another, surely legislation would have been instituted by now. Therefore, we leave the decision of when to clamp and collect the cord blood up to the preferences of the mother and her physician or midwife. In our experience, we have not found that the difference in time involved makes for a significant difference in collection.

MOHAMED GABALLA
Director, Cardiology Research
Sun Health Research Institute
Phoenix, AZ, USA

DAVID T HARRIS
Professor of immunobiology
Director, Stem Cell Bank
The University of Arizona
Tucson, AZ, USA

NATHAN COPELAND
Medical student, MD-Candidate Class of 2012
The University of Arizona
Tucson, AZ, USA

References

1 Meier C, Middelanis J, Wasielewski B *et al.* Spastic paresis after perinatal brain damage in rats is reduced by human cord blood mononuclear cells. *Pediatr Res* 2006;59:244–9.
2 Ceriani Cernadas JM, Carroli G, Pellegrini L *et al.* The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. *Pediatrics* 2006;117:e779–86.
3 Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. *JAMA* 2007;297:1241–52.
4 McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Sys Rev* 2008;(2):CD004074.
5 Neilson, JP. Cochrane update: effect of timing of umbilical cord clamping at birth of term infants on mother and baby outcomes. *Obstet Gynecol* 2008;112:177–8.

Discrepancies between histology and serology for the diagnosis of coeliac disease (1)

Editor – Sweis and colleagues showed discrepancies between histology and serology in the diagnosis of coeliac disease (CD) (*Clin Med* August 2009 pp 346–8), and suggest we reduce our reliance on serology testing in diagnosing and excluding CD. However, we feel there are major reasons to reconsider this.

The numbers reported here must be interpreted carefully: 10 out of 26 CD patients who received serologic testing were seronegative. This 38.5% occurrence of seronegative CD is misleading. In the spirit of Bayes theorem, the more common the condition we are testing, the greater the percentage of false negative results.[1] In this case, all 26 patients were selected due to the diagnosis of CD, meaning the prevalence in this group was already 100%. Therefore, this group is bound to have a high number of false negative tests. The authors correctly state that a small number of cases of CD will be missed by relying on serology alone, but the true prevalence is unknown, and this number is likely to be much lower than 38.5%.

In addition, the predictive value of using an ELISA-based method to detect tissue transglutaminase autoantibody (tTG) remains open to discussion. There are currently numerous tTG assays available, all with varying performances. The International tTG Workshop for CD performed head-to-head comparisons of various commercial and laboratory-based tTG assays. For this workshop, assays reported sensitivities ranging from 82% to 93%, underscoring the marked variability in assay performance.[2] Given these findings, the lack of positive serology in a proportion of their biopsy-proven coeliacs could be assay dependent.

Finally, even though intestinal biopsy is the gold standard method to diagnose CD, it is not without its short comings. The sensitivity of histology is largely dependent on the site and number of biopsy samples taken.[3,4] Negative histology often excludes a diagnosis of CD. However, a proportion of these patients have CD-like gastrointestinal symptoms, which might be attributed to the subtle changes seen in microscopic enteritis that could go undetected.[5]

In all, we agree that it is important not to rely on serology alone for the diagnosis of CD, but to allow serology to increase or decrease your estimation of risk of disease. However, considering the lifelong implications of a diagnosis of CD, one should still maintain a degree of suspicion and also take great care in interpreting villous atrophy in the absence of autoantibodies in any patient.

DEVASENAN DEVENDRA
Consultant physician and honorary senior lecturer
NHS Brent, Central Middlesex Hospital
and Imperial College, London

CHUKWUMA UDUKU
Research assistant and 6th year medical student
Department of Investigative Sciences
Imperial College, London

EDWIN LIU
Associate professor, pediatrics
Section of Gastroenterology,
Hepatology and Nutrition
The Children's Hospital,
University of Colorado at Denver

YANNOULLA WILSON
Laboratory manager, Autoimmune Serology
Northwest London Hospitals NHS Trust

References

1 Shapiro D. The interpretation of diagnostic tests. *Stat Methods Med Res* 1999; 8(2):113–34.
2 Li M, Yu L, Tiberti C *et al.* A report on the International Transglutaminase Autoantibody Workshop for Celiac Disease. *Am J Gastroenterol* 2009;104:154–63.
3 Bonamico M, Mariani P, Thanasi E *et al.* Patchy villous atrophy of the duodenum in childhood celiac disease. *J Pediatr Gastroenterol Nutr* 2004;38:204–7.
4 Pais W, Duerken D, Pettigrew N *et al.* How many duodenal biopsy specimens are required to make a diagnosis of celiac disease? *Gastrointest Endosc* 2008;67:1082–7.
5 Rostami K, Villanacci V. Microscopic enteritis: novel prospect in coeliac disease clinical and immuno-histogenesis. Evolution in diagnostic and treatment strategies. *Dig Liver Dis* 2009;41:245–52.

Discrepancies between histology and serology for the diagnosis of coeliac disease (2)

Editor – Discrepancies between histology and serology for the diagnosis of coeliac disease (CD) (*Clin Med* August 2009 pp 346–8)

are inevitable, given the fact that, even measurement of transglutaminase autoantibodies (TGAA), the latter now considered to be the most efficient single test for CD,[1,2] generated variable diagnostic accuracy in a workshop designated to compare test performance for TGAA among 20 institutions, comprising five commercial and 15 research and clinical laboratories. In that study six laboratories contributed sera from individuals with CD as defined by accepted clinical criteria including small bowel biopsy, and these were compared with healthy control sera from individuals not known to have CD or type 1 diabetes. Assays for TGAA included enzyme-linked immunosorbent assay (ELISA) and radiobinding assays (RBA). Laboratory sensitivity ranged from 69% to 93%, and specificity ranged from 96% to 100%. The highest sensitivity (93%) with 100% specificity was achieved by two radiobinding assays, and RBA identified sera from CD patients as positive with greater frequency than did ELISA. Nevertheless, ELISA assays together provided less variation in 'signal-to-noise' than did RBA. However, for the coeliac samples between different laboratories performing ELISA, linear correlation, r-squared, ranged from 0.4244 to 0.8882.3 What has also emerged is that the age-related differences documented in the clinical and histological stigmata of CD, have, as a corollary, a correlation between TGAA levels and degree of villous atrophy. This was shown in a study where severe villous atrophy (Marsh IIIB and IIIC) was significantly ($p<0.0001$) more prevalent in children than in adults. In that study, a significant correlation was also established between IgA TGAA titres and age (Pearson coefficient$=0.524$; $p<0.001$), and also between IgA TGAA titres and degree of villous atrophy (Spearman rho$=0.59$; $p<0.001$).[4] Accordingly, given the fact that concordance between histology and serology depends, not only on the performance and methodology of the laboratory performing the serological tests, but also on patient characteristics, histology should continue to be the 'gold standard' for diagnosis of CD.

OSCAR MP JOLOBE
Manchester Medical Society, Manchester

References

1 Lewis NR, Scott BB. Systematic review; the use of serology to exclude or diagnose celiac disease (a comparison of endomyseal and tissue transglutaminase antibody tests). *Aliment Pharmacol Ther* 2006;24:47–54.
2 AGA Institute. AGA Institute Medical Position Statement on the Diagnosis and Management of Celiac Disease. *Gastroenterology* 2006;131:977–80.
3 Li M, Yu L, Tiberti C *et al.* A report on the International Transglutaminase Autoantibody Workshop for Celiac Disease. *Am J Gastroenterol* 2009;104:154–163.
4 Vivas S, Ruiz de Morales JM, Fernandez M *et al.* Age-related clinical, serological, and histopathological features of celiac disease. *Am J Gastroenterol* 2008;103:2360–5.

In response

We would like to thank the respondents for their helpful insights and comments which offer several plausible explanations for the discrepancy we observed between serological and histological testing for coeliac disease (CD). The ELISA-based IgA anti-tissue transglutaminase (anti-tTG) assay used at Medway Hospital is typical of that used at many peripheral centres. Although an antibody radiobinding assay for measuring IgA antibodies to human tissue transglutaminase has been shown to achieve a sensitivity and specificity at least equivalent to endomysial antibody,[1] it is not readily available. It is therefore common practice to combine serological testing in order to improve sensitivity and specificity.[2] The positive and negative predictive value of combining IgA anti-tTG antibodies and IgA anti-endomysial antibodies has been reported to be over 95%.[3] A multicentre European study showed that out of 126 biopsy-confirmed cases with CD, eight (6.4%) had negative combined IgA anti-tTG (ELISA-based) and IgA anti-endomysial antibodies.[4] We accept that the IgA and IgG anti-gliadin antibody assay is no longer used in most centres due to reduced sensitivity and specificity, and serological testing at Medway hospital has since been changed to IgA and IgG anti-endomysial antbody and IgA and IgG anti-tissue transglutaminase. Furthermore, although none of the patients were known to be on a formal gluten free diet, it is possible that some may have reduced their gluten intake prior to serology testing.

We fully accept that our false negative rate for serology should be interpreted with caution and because of the small numbers, may overestimate the magnitude of the problem. Never the less, it would be surprising if this finding was unique to our hospital. There is often a long delay in diagnosis ranging from 4.9 to 11 years,[5,6] as illustrated by our case study and the increasing reliance on non-invasive testing means that patients will remain undiagnosed. What is clear is that we all agree that it is important for physicians to be aware of the more protean presentations of CD, the limitations of serology and the importance of a duodenal biopsy in making the diagnosis of CD.

RAMI SWEIS
Specialist registrar
St Thomas' Hospital, London

LEON PEE
Registrar
Queen Elizabeth the Queen Mother Hospital, Margate

GRAY SMITH-LAING
Consultant in gastroenterology
Medway Maritime Hospital

References

1 Williams AJ, Annis P, Lock RJ *et al.* Evaluation of a high-throughput second antibody radiobinding assay for measuring IgA antibodies to human tissue transglutaminase. *J Immunol Methods* 1999;228:81–5.
2 Lock RJ, Stevens S, Pitcher MC, Unsworth DJ. Is immunoglobulin A anti-tissue transglutaminase antibody a reliable serological marker of coeliac disease? *Eur J Gastroenterol Hepatol* 2004;16:467–70.
3 Hill I. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology* 2005;128:S25–32.
4 Collin P, Kaukinen K, Vogelsang H *et al.* Antiendomysial and antihuman recombinant tissue transglutaminase antibodies in the diagnosis of coeliac disease: a biopsy-proven European multicentre study. *Eur J Gastroenterol Hepatol* 2005;17:85–91.
5 Green PHR, Stavropoulos SN, Panagi SG *et al.* Characteristics of adult celiac disease in the USA: results of a national survey. *Am J Gastroenterol* 2001;96:126–31.
6 Lankisch PG, Martinez Schramm A, Petersen F *et al.* Diagnostic intervals for recognizing celiac disease. *Z Gastroenterol* 1996;34:473–7.