Author's Reply.

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change the paradigm in obstetrics that glomerular endotheliosis is a pathognomonic lesion found in renal biopsies from pre-eclamptic women.

The degree of proteinuria has traditionally been used to determine severity of disease,[3] and the authors hypothesise that the degree of glomerular endotheliosis might be a better indicator of the state of risk of pregnancy complications associated with pre-eclampsia than proteinuria has proved to be.[1] It would be interesting to see their data on urinary protein excretion, and its use as marker of the degree of endotheliosis, analysed for comparison with Cystatin-C (besides creatinine and urate). Tables 1, 2 and 3, in the additional paper, suggest that a positive correlation between urinary protein excretion with the degree of endotheliosis is probably present.[2] Besides, when the degree of endotheliosis was rated as 'one', the values of Cystatin-C were mostly within normal values. So it might be questionable if the use of Cystatin-C, instead of the use of serum creatinine and urinary protein excretion, should be recommended for pre-eclampsia monitoring.

The authors state that determining serum Cystatin-C might considerably reduce the need for renal biopsy in pre-eclampsia.[1] We believe that there is no need to perform renal biopsy in women with pre-eclampsia, except in rare occasions. If there is doubt about the diagnosis, pre-eclampsia should be overdiagnosed[3] and, depending on the clinical presentation and outcome, the presence of renal disease could be defined postpartum.

We also believe that the pre-eclamptic state should be evaluated in association with maternal and neonatal outcome. Fetal monitoring may determine pregnancy interruption before delivery is indicated based on the mother's risks. It would be worth noting to see their data on the newborn.

References

1. Strevens H, Wide-Swensson D, Grubb A, et al. Serum Cystatin-C reflects endotheliosis in normal, hypertensive and pre-eclamptic pregnancies. *Br J Obstet Gynaecol* 2003;**110**:825–830.
2. Strevens H, Wide-Swensson D, Hansen A, et al. Glomerular endotheliosis in normal pregnancy and pre-eclampsia. *Br J Obstet Gynaecol* 2003;**110**:831–836.
3. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. *Am J Obstet Gynecol* 2000;**183**:s1–s22.

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Glomerular endotheliosis in normal pregnancy and pre-eclampsia

Sir,

I read with dismay the article in your September issue by Dr Strevens *et al.* (Glomerular endotheliosis in normal pregnancy and pre-eclampsia, BJOG 110, 831–6, 2003).

As a practising nephrologist with both clinical and research interests in medical disorders of pregnancy, I must comment that there are *no* indications to perform renal biopsy in normal pregnant women, a procedure with acknowledged risks even in the best of hands and even with the most advanced imaging techniques—risks which include bleeding with a need for transfusion, and possible nephrectomy, as well as damage to adjacent organs and the complications that can arise from this. This is a procedure that, even in the non-pregnant, should be performed only when the information to be gained is essential to a major therapeutic decision. At least the same level of caution should be applied to pregnancy, and the conduct of renal biopsy in a normal woman in late pregnancy is ethically unjustifiable even with patient consent. The collection of two cores of tissue in all subject, and three in a proportion, increases the risks even further.

In my own practice, and I am sure in the practice of most nephrologists who see large numbers of pregnancies complicated by medical disorders, renal biopsy is rarely performed, and then only when the benefits to the individual patient clearly outweigh the risks of the procedure. These decisions are made on clearly defined, and generally agreed clinical grounds, and the article by Strevens *et al.* adds nothing of substance to this decision-making process. The presence or absence of glomerular endotheliosis changes nothing in the care of a pregnant woman.

Those of us who conduct active clinical research have an additional duty of care, not only to our patients with renal disease, but also to the general public, who look to us as responsible ethical practitioners, and who trust us to make appropriate decisions affecting their health. Clinical research is essential to increasing the body of medical knowledge, but studies of this nature do not support the accepted ethical principles of our profession, and acceptance of them gives credence to a standard of care that most practitioners would not consider acceptable.

Eileen D. M. Gallery

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Author's Reply

Sir,

We begin with some general points. We agree there were ethical issues in embarking on our study but there would also have been ethical issues in refraining from doing it and making assumptions about the biopsy picture in pregnancy. Renal biopsy has been used in the past to 'verify' the diagnosis of pre-eclampsia. However, the *presence* of endotheliosis is not characteristic of pre-eclampsia, although the *degree* may be more pronounced. Postpartum biopsy studies may have missed early regression of some glomerular lesions and erroneously diagnosed healing stages a renal disease. The consequence of subjecting sick patients to the risk of renal biopsy unnecessarily, or diagnosing renal disease erroneously, may be important. Ultimately, patients have the most to lose from limiting our knowledge of their conditions, and our concern for them persuaded us of the necessity of this study. We are also grateful for the altruism of the 12 healthy pregnant controls. The first author's thesis (*Blood pressure, renal functional and structural changes, in normal and preeclamptic pregnancy*, http://www.lub.lu.se.dissdb/) devotes a chapter to the ethical aspects.

Professor Lindheimer, an authority on the renal pathology in pre-eclampsia, accepts that 'evaluation of the renal biopsy, performed during pregnancy or the immediate puerperium has enhanced our understanding of the pathophysiology of pre-eclampsia immensely'[1] and he hopes 'that future progress in elucidating the

pathophysiology of pre-eclampsia will lead to the development of clinically useful predictive and diagnostic tests'.[2] Renal biopsy studies in severe early-onset pre-eclampsia at a gestational age of 30 (3) weeks, correlating biopsy findings with markers for 'pure pre-eclampsia'[3] are cited and accepted by him.[2] The one patient who experienced complications had clinical indications for the biopsy as recommended by Lindheimer. We chose to include her in the report because of the complications she developed, namely, persistent bleeding from two vessels less than 1 mm in diameter, which normally should have contracted immediately. She was the last to be included.

Even if the renal biopsy is not regarded as diagnostic, it certainly has been interpreted as able to 'correctly establish' or ''distinguish 'pure eclampsia''' from other conditions.[1] This might have led to an increase in renal biopsies in pre-eclampsia as safer techniques develop. Our Research Ethics Committees in Sweden are recognised to be among the world's strictest, and also insist on the highest scientific quality of approved studies. They would not have approved uncontrolled research. They have appreciated the necessity of not simply making assumptions about a control group, but at long last, finally establishing the renal histology of normal pregnancy for scientific comparison with the pathology of pre-eclampsia.

Surprisingly, the only effort previously made to establish the renal histology of normal pregnancy seems to be the classical antepartum renal biopsy study from 1960 by Pollak and Nettles,[4] including five healthy pregnant controls, all with blood pressure levels lower than 120/75 and none showing signs of endotheliosis. Relating the degree of structural change to the degree of functional change (then to S-urate levels) was first attempted in this study, where even with blind biopsies and experimental biopsy techniques, complications were limited to one case of gross haematuria and four patients experiencing some degree of pain ($n = 59$).

Having access to modern and safe biopsy techniques, we do not recognise the complication rates described in the letters. At our centre well over 1000 renal biopsies have been performed without renal complications, the clinically indicated biopsy in our study being the single exception. The outdated complication frequencies cited by Lindheimer appear to refer to a review from 1987,[3] in a debate on *clinical* indications for biopsies, citing reports from 1975 and 1977 of studies from Lindheimer's own institution and other centres from 1964 and onwards, as well as studies commencing in 1954.

Even then, concurrent more favourable reports and 'excellent statistics' were acknowledged to be related to 'technical skills', 'experience with the procedure' and 'prebiopsy assessment' in an antepartum study with only one case of clinical perirenal haematoma out of 111.[6] Since then, biopsy techniques have vastly improved, notably in our group, drawing on the traditions of Dr Claus Brun, who developed the technique in 1951. Modern renal biopsy studies in pre-eclampsia have similarly not reported any complications and have concluded the procedure to be safe in the research setting.[7–10] Even so, our patients were told that renal haematoma or haematuria could occur at a rate of 1/59–111.[4,6] We do not wish to belittle the dangers of renal biopsy.

We understand that Professor de Swiet and Dr Lightstone continue to recommend renal biopsy for the diagnosis of intrinsic renal disease in the high risk patient with renal failure in pregnancy remote from term. We agree that the complication frequencies, following these recommendations, are appalling,[11] and that renal biopsy is 'a morbid procedure'. The whole point of our studies was to once and for all abolish this use of renal biopsy in pregnancy. Seldom is not little enough. If these high risk patients are avoided, it has long been recognised that the risks of renal biopsy are not greater in pregnancy.[6,12] We have a totally different experience than de Swiet describes.

It grieves us deeply that Professor Gallery seems to believe our studies have added nothing of substance to the decision-making process in the intricate, difficult, often life-changing decisions concerning the pre-eclamptic patient. We are confronted daily with such decisions.

Professor Gallery herself advises: 'Close monitoring of maternal and fetal welfare will help to determine the optimum time for delivery.'[13] But monitoring with what? We have adequate methods of monitoring the wellbeing of the fetus, but cannot predict deterioration in maternal condition.

Clinical indications of maternal decline are often late markers of already impending complications and imminent catastrophe. Every clinically practising obstetrician appreciates this. This is why pre-eclampsia is still the leading cause of maternal mortality. To try to achieve a diagnosis through renal biopsy in these patients is unacceptable but is still being done in some countries, just because they happen to develop renal failure before they develop other symptoms.

Our studies show the renal process of endotheliosis, developing in a continuum between normal late pregnancy and severe pre-eclampsia, with increased risk to the mother when more pronounced. We have related it to a simple blood test, S-Cystatin C, which can instantly provide us with information on how far the process has developed and how rapidly. To disregard these studies as 'adding nothing' is unfair.

In response to Professor Akbari, we accept that it is well established that the glomerular filtration rate rises in the first trimester of pregnancy, but also that it decreases at term.[14–16] Our previous studies[17] verify these changes in glomerular filtration rate determined by isohexol clearance, which correlate to S-Cystatin C levels. S-Cystatin C levels decrease in early pregnancy, but rise slightly at term. The reason S-creatinine does not rise at term in every pregnancy, or for that matter in many pre-eclamptic patients, is simply that it is a less sensitive marker.

The correlation between isohexol clearance and S-Cystatin C differs in pregnant women, over-estimating decreases in glomerular filtration rate if non-pregnant reference ranges are used. If reference ranges for pregnant women are used, S-Cystatin C reflects glomerular filtration rate closely. The altered filtration in pregnancy, indicated in neutral dextran studies,[18] is in itself also of interest. Why is this 13 kDa positively charged molecule filtered differently in pregnancy?

We believe that changes in the glomerular filtration rate towards term in pregnancy are caused by endotheliosis, in which case they could be paralleled by a loss of glomerular barrier charge-selectivity in addition to a change in size-selectivity.[19–20] The filtration of a positively charged molecule would then be more restricted than that of an uncharged molecule of equal size.

S-Cystatin C could therefore be reflecting both parallel changes, which endotheliosis causes to glomerular filtration. The fact that S-Cystatin C in this respect over-estimates decreases in the glomerular filtration rate of fluids if non-pregnant reference intervals are used is less important than the fact that it closely reflects the degree of endotheliosis and thus supplies information on pathology without requiring biopsy.

In response to Dr Poli de Figueiredo *et al.*, levels of U-albumin in this study were not significantly correlated with estimated glomerular volume even when log-transformed values or non-parametric tests were used or after adjustment for collection time or urine concentration (using the U-albumin/U-creatinine ratio).

U-albumin is an easily accessible marker of the pre-eclamptic state of pregnancy risk even if it does not describe the degree of severity. S-Cystatin C performs better as a marker for pre-eclampsia defined as a diastolic blood pressure >90 mmHg and the presence of significant albuminuria, than S-urate or S-creatinine.[21] We agree that results concerning fetal monitoring

in these patients are highly interesting. We hope to be publishing such data presently.

References

1. Gaber LW, Lindheimer MD. Pathology of the kidney, liver and brain. In: Lindheimer MD, Roberts JM, Cunningham FG, editors. *Hypertensive Disorders in Pregnancy*. Stamford, Connecticut: Appleton & Lange, 1999:201–227.
2. Friedman SA, Lindheimer MD. Prediction and differential diagnosis. In: Lindheimer MD, Roberts JM, Cunningham FG, editors. *Hypertensive Disorders in Pregnancy*. Stamford, Connecticut: Appleton & Lange, 1999:201–227.
3. Weiner CP, Bonsib SM. Relationship between renal histology and plasma antithrombin III activity in women with early onset pre-eclampsia. *Am J Perinatol* 1990;**7**:139–143.
4. Pollak VE, Nettles JB. The kidney in toxaemia of pregnancy: a clinical and pathologic study based on renal biopsies. *Medicine* 1960;**39**: 469–526.
5. Lindheimer MD, Davison JM. Renal biopsy during pregnancy. ''To b or not to b.'' *Br J Obstet Gynaecol* 1987;**94**:932–935.
6. Packham D, Fairley KF. Renal biopsy: indications and complications in pregnancy. *Br J Obstet Gynaecol* 1987;**94**:935–939.
7. Nochy D, Heudes D, Glotz D, Lemoine R, Gentric Dm Bruneval P, Bariety J. Preeclampsia associated focal and segmental glomerulosclerosis and glomerular hypertrophy: a morphometric analysis. *Clin Nephrol* 1994;**42**:9–17.
8. Gartner HV, Sammoun A, Wehrmann M, Grossmann T, Junghans R, Weihing C. Preeclamptic nethropathy — an endothelial lesion. A morphological study with a review of the literature. *Eur J Obstet Gynecol Reprod Biol* 1998;**77**(1):11–27.
9. Khedun SSM, Naicker T, Moodley J. Relationships between histopathological changes in post partum renal biopsies and renal function tests of African women with early onset pre-eclampsia. *Acta Obstet Gynecol Scand* 2000;**79**(5):350–354.
10. Murakami S, Saitoh M, Kubo T, Koyama T, Kobayashi M. Renal disease in women with severe preeclampsia or gestational proteinuria. *Obstet Gynecol* 2000;**96**(6):945–949.
11. Kuller JA, D'Andrea NM, McMahon MJ. Renal biopsy and pregnancy. *Am J Obstet Gynecol* 2001;**184**:1093–1096.
12. Lindheimer MD, Spargo BH, Katz AI. Renal biopsy in pregnancy-induced hypertension. *J Reprod Med* 1975;**15**:189–194.
13. Gallery ED. Hypertension in pregnancy. Practical management recommendations. *Drugs* 1995;**49**(4):555–562 (April).
14. Davison JM, Hytten FE. Glomerular filtration during and after pregnancy. *Br J Obstet Gynaecol* 1974;**81**:588–595.
15. Davison JM, Dunlop W, Ezimokhai M. 24-hour creatinine clearance during the third trimester of normal pregnancy. *Br J Obstet Gynaecol* 1980;**87**:106–109.
16. Conrad KP, Lindheimer MD. Renal and cardiovascular alterations. In: Lindheimer MD, Roberts JM, Cunningham FG, editors. *Hypertensive Disorders in Pregnancy*. Stamford, Connecticut: Appleton & Lange, 1999:263–326.
17. Strevens H, Wide-Swensson D, Torffvit O, Grubb A. Serum cystatin C for assessment of glomerular filtration rate and altered filtration process in pregnancy. *Scan J Clin Lab Invest* 2002;**62**(2):141–147.
18. Roberts M, Lindheimer MD, Davison JM. Altered glomerular permselectivity to neutral dextrans and heteroporous membrane modelling in human pregnancy. *Am J Physiol* 1996;**270**:F338–F343.
19. Naicker T, Randeree IGH, Moodley J, et al. Correlation between histologic changes and loss of anionic charge of the glomerular basement membrane in early-onset preeclampsia. *Nephron* 1997;**75**:201–207.
20. Moran P, Baylis PH, Lindheimer MD, Davison JM. Glomerular ultrafiltration in normal and preeclamptic pregnancy. *J Am Soc Nephrol* 2003;**14**(3):648–652 (March).
21. Strevens H, Wide-Swensson D, Grubb A. Serum cystatin C is a better marker for preeclampsia than serum creatinine or serum urate. *Scand J Clin Lab Invest* 2001;**61**(7):575–580.

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Editor's note

Our correspondents raise at least three issues. They question whether the research participants had been correctly informed of the risks of renal biopsy. The Scandinavian authors reply that in their hands, in the absence of severe disease, the risks are very low, and that participants were therefore correctly informed. The inclusion of the final patient with severe pre-eclampsia who experienced significant complications seems to have confused the issue. She was exposed to a higher risk and should have been informed of this. The authors defend her biopsy on the grounds that it had been indicated for clinical, albeit now obsolete, reasons. This should have been made clearer in the paper.

The second issue is whether pregnant women should be allowed to take such risks for the sake of contributing to research. Competent adults are normally permitted to decide for themselves whether to participate in non-therapeutic research, but the baby cannot decide for itself and I am therefore surprised that the research ethics committee (REC) approved the study. Perhaps they argued, somewhat implausibly, that there were no net risks to the baby. Perhaps they reasoned that parents are the best placed to decide for their unborn children - we allow them to smoke for example. If the parents felt they were gaining a warm altruistic glow from participation, perhaps they should be allowed to take a small risk with their children. Perhaps the committee simply forgot that it was considering non-therapeutic research in a vulnerable group. It would not be the first REC to make an unethical decision. We have commissioned a commentary on this topic for a future issue.

Finally BJOG has been accused of impropriety in publishing the results. I reject this. It is a good principle that unethical research should not be published, but BJOG does not perform a new ethical review of papers we receive; we rely on properly constituted research ethics committees. The present paper had been with us for some time, and the original referee had raised most of these issues. As a result the editors sought a second opinion from a clinician with experience in medical ethics, who also expressed some concerns, but felt that if the REC had been properly constituted the paper should be published. My predecessor John Grant agreed, and after revisions accepted the paper. I think he was correct. Whether the study was right or wrong, it would surely have been wrong, after it was completed, to have effectively restricted future access to these data. My only regret is that we did not highlight the ethical dilemmas with an editorial or commentary at the time of the original publication. I hope that publication of this extended correspondence, partly makes amends.

Jim Thornton
Editor-in-Chief