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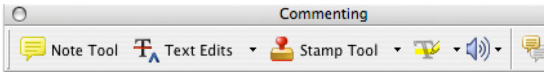
<table>
<tr><th colspan="2">PDF ANNOTATIONS</th></tr>
<tr><th>Adobe Reader version 9</th><th>Adobe Reader version X and XI</th></tr>
<tr><td>When you open the PDF file using Adobe Reader, the Commenting tool bar should be displayed automatically; if not, click on ‘Tools’, select ‘Comment & Markup’, then click on ‘Show Comment & Markup tool bar’ (or ‘Show Commenting bar’ on the Mac). If these options are not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than 9 or the PDF has not been prepared properly.
 

(Mac)
PDF ANNOTATIONS (Adobe Reader version 9)

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 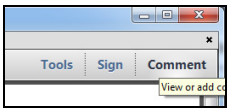

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 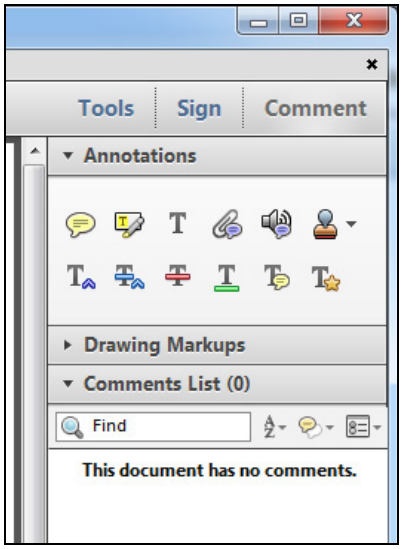
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HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Insert text	Click the 'Text Edits' button  on the Commenting tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner.	Click the 'Insert Text' icon  on the Comment tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on '_'  in the top right-hand corner.
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Remove text	Click the 'Text Edits' button  on the Commenting tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.	Click the 'Strikethrough (Del)' icon  on the Comment tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.
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Leave a note/ comment	Click on the 'Note Tool' button  on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.	Click on the 'Add Sticky Note' icon  on the Comment tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.

HOW TO...		
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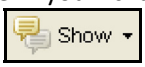
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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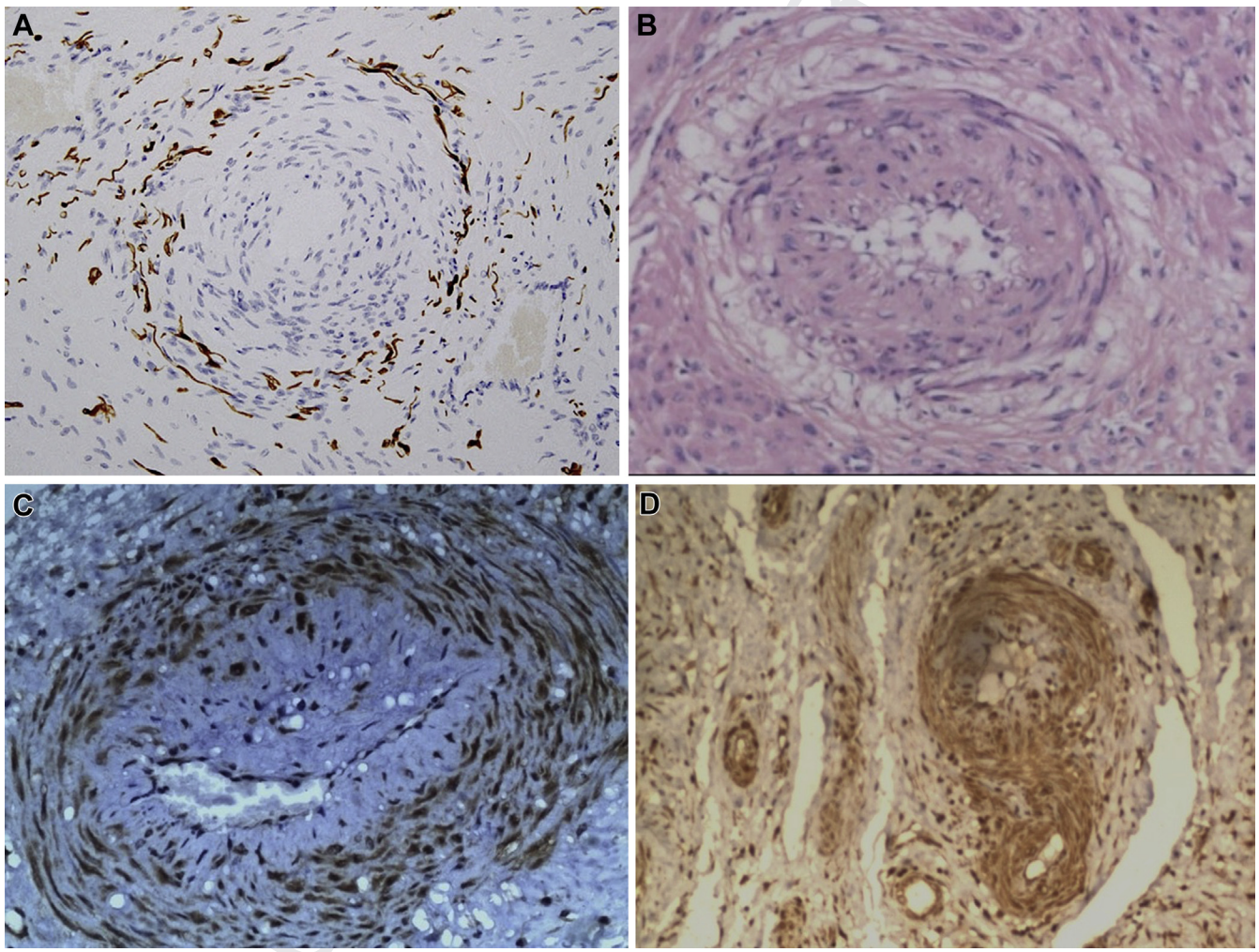
REPLY

In 1953, Sophian reported experiments inflating balloons in rabbit uteri and watching their kidneys turn white; he released the stretch, and renal blood flow was promptly restored.[1] Dividing the uterorenal nerves abolished the reflex. He proposed that activating uterorenal nerves (cf, cardiorenal, hepatorenal, lienorenal, etc) was the mechanism for renal cortical ischemia in preeclampsia. On his evidence, preeclampsia is a disorder of uterine stretch.

Two recent observations have prompted renewed interest in this hypothesis.[2–4] First, prepregnancy injuries to uterine vasomotor nerves release cytokines and growth factors that result in the regeneration of abnormal injured nerves and hyperplasia of adjacent, denervated, arteriolar walls in preeclampsia[2] (Figure, A and B).

Second, these injuries induce specific, purinergic, P2X3, stretch receptors in the walls of uterine arterioles, providing a direct mechanism for activating uterorenal nerves that redistribute renal blood flow from the cortex to the medulla[1,3] (Figure, C and D). Removal of the stretch at delivery reverses these renal effects, and the hypertension resolves promptly.

FIGURE
Injured uterine arterioles in obstetric and gynecologic syndromes



A, A narrowed uterine arteriole in a painful, non pregnant uterus (anti-S100, ×100) demonstrates a halo of injured nerves around the circumference of a narrowed arteriole with irregular hyperplasia of the tunica media. **B,** A narrowed, uterine arteriole in a pregnant uterus demonstrates a halo of hyalinized cells around the circumference of an injured arteriole with irregular hyperplasia of the arteriolar wall (hematoxylin and eosin, ×100). During pregnancy, injured nerves cannot extend from the isthmus of the uterus to the placental bed, although the injured arterioles and nerve sheaths can do so, accounting for the similar, although different, appearances in pregnant (B) and nonpregnant (A) uteri. **C and D,** Purinergic, P2X3, stretch receptors (*brown*) are induced in arteriolar walls and injured myometrium in pregnancy hysterectomy specimens removed for postpartum hemorrhage (anti-P2X3, ×100).

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Does Professor Brosens consider a prepregnancy injury to uterine nerves a plausible explanation for defective deep placentation in the Great Obstetric Syndromes, and might it better explain their relationship to some gynecologic syndromes[4,5] (Figure, A–D)?

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The authors report no conflict of interest.

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