

## It's time to pay attention to the endometrium, including the nucleolar channel system

*To the Editor:*

In the context of the excellent Views and Reviews devoted to the endometrium (1), Dr. Bruce A. Lessey offers a thorough analysis of 186 publications that are of significance to the window of implantation (WOI) (2). We feel this already exhaustive effort needs to be expanded further. Although one histological hallmark of midluteal endometrium—pinopodes (whose significance as markers of endometrial receptivity has been questioned)—is reviewed in detail, another, the nucleolar channel system (NCS), went unmentioned. The presence of NCSs distinctly marks the midluteal phase of human endometrium overlapping with the WOI.

NCSs were identified over half a century ago using electron microscopy and can now be readily detected by marker proteins using indirect immunofluorescence (3). These 1  $\mu\text{m}$  sized organelles are found exclusively in the nuclei of human endometrial epithelial cells of the secretory phase. NCSs are specific to healthy human endometrium, being absent from other hormone-sensitive tissue (such as breast epithelium), from endometrial carcinoma specimens, and from baboon endometrium. The presence of NCSs peaks during

cycle days LH+5 to LH+10 (menstrual cycle days 19–24) and subsequently trails off (3, 4). NCSs are absent before LH+4, after LH+13, and during the proliferative phase. In fact, their midluteal/WOI presence is so robust that it is independent of fertility status (5).

Despite a lack of functional definition, NCSs are cell biological marvels with a unique protein composition and as membranous organelles in the otherwise membrane-free cell nucleus. Now that they can be easily detected in endometrial biopsy specimens, NCSs should not be discounted as potential markers of the WOI and certainly deserve an honorable mention.

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*Reply of the Authors:*

We thank Nejat et al. for their letter to the editor regarding the new Views and Reviews feature in the September issue of *Fertility and Sterility* about the endometrium. They note our omission of the nucleolar channel system (NCS) as one of the ultrastructural entities of a receptive endometrium. Indeed, there are 22 references on PubMed dating back to 1965 on these fascinating and unique subcellular features of midsecretory endometrium. I was aware of the NCS during endometrial development, and we discussed the potential importance of these structures (complete with photomicrographs) in the latest version of Yen and Jaffe's textbook in the chapter entitled "The structure, function and evaluation of the female reproductive tract" (1). It is likely that I left out other favorite endometrial moieties as well, and I apologize to Nejat et al. and to everyone else who might find that the article falls short of the mark.

As Nejat et al. point out, the expression pattern of NCS, while present in the midsecretory phase, is unperturbed in the endometrium of women with unexplained infertility and present regardless of fertility status (2). In thinking about what to include in an article about endometrial receptivity (with too many references), I considered that the ideal biomarker would have functional significance to the process of implantation. By that, I also inferred that the loss of that biomarker would logically be associated with a deficit as

evidenced by infertility or pregnancy loss. Since this particular biomarker does not appear to bear that attribute, I did not include it. In thinking about this further in response to Nejat et al.'s letter, I think it is indeed unusual and even unlikely that a P-mediated event (directly or indirectly) (3) would not be affected by endometriosis or other gynecologic disorders that have been shown to cause P resistance in some women (4). Such a robust biomarker certainly deserves future study and is a feature that might be examined in the luteal phase defect model of endometrial development on which Dr. Steven Young and Dr. Marc Fritz at the University of North Carolina have been working (5). There must be levels of P below which the NCSs do not correctly assemble or form, and this model would certainly address that question.

I hope that readers of this exchange will now go and read more about these interesting structures and appreciate, as I do, the ever-growing complexities and mysteries of the human endometrium.

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