ponent of the flow velocity waveform can exist when the overall velocities are reduced. This is important because absolute velocities have been shown to be a more sensitive indicator of angiogenesis within the ovary than the pulsatility index (4). Absolute velocities in cm/second require measurement of the angle between the long axis of the vessel and the Doppler beam unless measurements are taken from an intense area of angiogenesis, when peak velocity or time average maximum velocity has been shown to be reproducible (5). Unfortunately, no data on absolute velocities in the paper Rubinstein et al. is available, for if the main ovarian artery was sampled, angle correction would have had to be made.

The authors have clearly demonstrated in a randomized, placebo-controlled study that aspirin is associated with improved ovarian responsiveness. However, we do not feel this paper is consistent with the published literature on resistance to flow in the ovarian vessels and, therefore, we must question whether they successfully sampled the ovarian artery or any other ovarian vessel. Until a more detailed explanation of the methodology is obtained, their rationale for the effect of aspirin on ovarian responsiveness must be questioned.

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Reply from Authors:

We appreciate your interest in our article (1) and hope the following methodological explanations would help you.

For ultrasound examination, the uterine artery was identified, and sample volume was adjusted to encompass the entire vessel. The system was switched to mixed-mode operation in which the two-dimensional image and the range-gated pulsed Doppler operated in a quasi-simultaneous format. Flow velocity waveforms were displayed at a selectable sweep speed between 1 and 1-0 cm/seg. Doppler shifts <100 Hz were eliminated by a high-pass filter. Once a good-quality waveform was obtained—based on audio and visual recognition, and maximum measured velocity—the image, including ≥ 3 waveforms, was frozen. A real-time image of the vessel was obtained and the Doppler beam line of insonation was adjusted so that it crossed the long axis of the vessel at as small an angle as possible. Left and right arteries were subject to the same procedure.

Then, a sagital section was obtained to gain information about the ovaries' position. The transducer head was directed into the vaginal vault lateral fornix and rotated 90 degrees. Lateral to and below the ovaries, a shape of a longitudinal vessel could be identified as the ovarian artery. With experience, it is possible to perform Doppler measurements in this vessel (2). Because a range-gated, pulsed Doppler system was used, only signals from the ovarian artery were received with no possibility of overlapping signals from other vessels. Waveforms were outlined automatically and a built-in computer program calculated the values afterwards.

The pulsatility index (PI) was chosen to reflect blood flow impedance distal to the point of sampling (3); it has been shown to be the most accurate current method of assessing flow impedance (4), and it can even be used when there is absent or reversed flow in diastole. The PI values can be calculated independently from the angle between Doppler beam and the course of the vessel. Because in the early cycle days the end-diastolic blood flow velocity approaches 0, A/B ratio would alter toward infinite, whereas resistance index would approach 1. Only PI can suitable quantify these signals. Furthermore, PI not only uses maximum peak flow velocity but it also takes into account the mean flow during the entire cardiac cycle.

Some authors used PI to analyze blood flow impedance and have found ovarian arteries' PI mean values of 2.5 (5), and between 2.71 and 3.32 (2) before oocyte retrieval with a marked increase of the diastolic blood flow velocity towards the end of cycle stimulation.

It is well known that there are strongly different opinions as regards the interpretation of Doppler findings. But observations can differ according to the observers and also according to the parameters to be taken into consideration to draw conclusions and provide overall information. For these reasons, we consider that it is very important that observations should be performed by the same observer in all cases—a situation we complied with.

We agree that it would be of great importance to repeat the same experience measuring the U.S. parameters proposed by Dr. Sladkevicius, but we also believe that conclusions cannot be based only on ultrasound findings but rather on an association of other multiple facts, which we have detailed in our discussion (1) and in our replies published in this same section.

We would like to thank you and the many authors that

have contacted us through this section as well as personally asking for further details and information regarding our study. We value serious debate, objections, questions, and the exchange of opinions in the belief that they are a highly important path for scientific progress.

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What Is the Threshold Value for Serum Estradiol Levels Associated With Adverse IVF Outcomes?

To the Editor:

I read with great interest the article by Sharara et al. (1) published in the September 1999 issue of Fertility and Sterility. There is still debate on the impact of high estradiol (E_2) levels on the day of hCG administration on implantation/pregnancy rates in patients undergoing IVF treatment. The authors concluded that peak E_2 levels of >3,000 pg/mL were not detrimental to IVF outcome in 106 patients undergoing the first IVF cycle and suggested that the threshold might be >5,000 pg/mL. As most of the studies had small sample size (2), it is difficult to draw a firm conclusion. I would like to bring to your attention the results of a retrospective study (3) in my unit involving 1,122 women of age <40 years undergoing their first IVF cycle.

Estradiol levels on the day of hCG were categorized into three groups: group A <10,000 pmol/L; group B 10,000–20,000 pmol/L; and group C >20,000 pmol/L (conversion factor: 3.67). In fresh cycles, group A had significantly lower pregnancy rate (PR) per transfer (16.2% vs. 23.7%, respectively, $P=.005$, χ^2) and implantation rate (8.7% vs. 11.7%, respectively, $P=.037$, χ^2), when compared with group B. PR per transfer in group C was significantly lower than group B (12.1% vs. 23.7%, $P=0.049$, χ^2) and group C had the lowest implantation rate (6.4%). In FET cycles, implantation rates of groups A, B, and C were similar (7.5%, 8.1%, and 9.6%, respectively) and PRs were also comparable in all groups. High yield of oocytes (>15) was not associated with adverse outcome in the fresh IVF cycles.

The above results give further support to the suggestion that the E_2 threshold might be >5,000 pg/mL. The debate, however, may still continue as the mechanism of high E_2 levels leading to impaired implantation is unclear (4).

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Reply of the Authors:

We would like to thank Dr. Ng for the letter concerning our recent manuscript (1). Because his manuscript is still in press, we are unable to comment on his findings, but we are encouraged by his retrospective study evaluating 1,122 women aged <40 years (2). His results in group C (>20,000 pmol/L, i.e., >5,449 pg/mL) that pregnancy rates (PRs) are lower compared with group B (with a *P* value [.049] that is barely statistically significant) are in agreement with our hypothesis that IVF outcome is not reduced until peak E_2 is >5,000 pg/mL (1, 3). In addition, we are curious about the lower IR and PRs in group A (<10,000 pmol/L, <2,724 pg/mL), and wonder whether this group may include poor responders or some patients with multiple prior IVF failures. This hopefully will be clarified when the article is published. It is unfortunate that the number of cycles performed in each group was not provided in Dr. Ng's letter.

The results of Dr. Ng's retrospective study will hopefully shed more light on the debatable role of high E_2 in IVF outcome, especially because it is the largest study to date (2). The identical IR and PRs in the three groups when the FET data are analyzed prove that there indeed is a lower IR and PR when E_2 levels are beyond a certain threshold level. We