Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium

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Objective: To examine whether thin endometria can be improved by increasing uterine radial artery (uRA) blood flow.
Design: A prospective observational study.
Setting: University hospital and city general hospital.
Patient(s): Sixty-one patients with a thin endometrium (endometrial thickness [EM] <8 mm) and high radial artery-resistance index of uRA (RA-RI ≥0.81).
Intervention(s): Vitamin E (600 mg/day, n = 25), l-arginine (6 g/day, n = 9), or sildenafil citrate (100 mg/day, intravaginally, n = 12) was given.
Main Outcome Measure(s): EM and RA-RI were assessed by transvaginal color-pulsed Doppler ultrasound.
Result(s): Vitamin E improved RA-RI in 18 (72%) out of 25 patients and EM in 13 (52%) out of 25 patients. L-arginine improved RA-RI in eight (89%) out of nine patients and EM in six (67%) patients. Sildenafil citrate improved RA-RI and EM in 11 (92%) out of 12 patients. In the control group (n = 10), who received no medication to increase uRA-blood flow, only one (10%) patient improved in RA-RI and EM. The effect of vitamin E was histologically examined in the endometrium (n = 5). Vitamin E improved the glandular epithelial growth, development of blood vessels, and vascular endothelial growth factor protein expression in the endometrium.
Conclusion(s): Vitamin E, l-arginine, or sildenafil citrate treatment improves RA-RI and EM and may be useful for the patients with a thin endometrium. (Fertil Steril® 2010;93:1851–8. ©2010 by American Society for Reproductive Medicine.)

Key Words: Thin endometrium, uterine blood flow, radial artery, vitamin E, sildenafil citrate

Adequate growth of the endometrium is indispensable for successful pregnancy. We often see patients with a thin endometrium, which may be caused by impairment of the normal process of endometrial growth. Low pregnancy rates are noted in patients with a thin endometrium (1–5). However, improving endometrial growth in patients with a thin endometrium is very difficult. In addition, little information is available regarding the factors responsible for impaired endometrial growth in patients with a thin endometrium.

Very recently, we showed the pathophysiological features of thin endometrium and suggested that a thin endometrium may be due to high blood flow impedance of uterine radial arteries, which are in the lower extremity of uterine arteries (5). Uterine blood flow is an important factor for endometrial growth (6, 7). Interestingly, we found that blood flow impedance of uterine radial arteries remains high throughout the menstrual cycle in patients with a thin endometrium, suggesting that high blood flow impedance of uterine radial arteries is associated with poor endometrial growth in patients with a thin endometrium (5). In our recent report (5), we raised our hypothesis for the pathophysiology of thin endometrium as follows: high blood flow impedance of uterine radial arteries, which could be a trigger, impairs the growth of the glandular epithelium and results in a decrease in vascular endothelial growth factor (VEGF) expression, which is a key factor for regulating angiogenesis in the human endometrium (8–10). Low VEGF levels cause poor vascular development, which in turn decreases blood flow in the endometrium. The vicious circle leads to a thin endometrium. Thus, it is likely that high blood flow impedance of uterine radial arteries is involved in the etiology of a thin endometrium. We therefore decided to study whether thin endometria can be improved by increasing uterine radial artery blood flow.

For this purpose, we focused on vitamin E and potential nitric oxide (NO) donors such as l-arginine and sildenafil

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citrate to increase uterine radial artery blood flow. Vitamin E has been shown to improve capillary blood flow in a variety of organs not only by inhibiting the breakdown of lipids in red blood cell membranes (11, 12) but also by protecting the endothelium from oxidative stress (13, 14). NO release from vascular endothelial cells leads to the relaxation of vascular smooth muscle mainly by activating cyclic guanosine monophosphate (cGMP) (15). Sildenafil citrate, a type 5 specific phosphodiesterase inhibitor, prevents the breakdown of cGMP and potentiates the effect of NO on vascular smooth muscle (16). L-arginine, a substrate of NO, increases hepatic and limb blood flow (17, 18). The present study was undertaken as a pilot study to investigate whether vitamin E, l-arginine, or sildenafil citrate treatment has a potential to increase the blood flow of uterine radial arteries and to improve endometrial growth in patients with a thin endometrium.

MATERIALS AND METHODS

The project was reviewed and approved by the Institutional Review Board of Yamaguchi University Graduate School of Medicine. Informed consent was obtained from the patients before collection of any tissue samples for this study.

Patients

A total of 61 women with a history of infertility, who had both a thin endometrium (endometrial thickness <8 mm) and high blood flow impedance of uterine radial arteries (radial artery-resistance index [RA-RI] ≥0.81), were recruited into this study. Endometrial thickness and uterine RA-RI were measured in the late follicular phase (1–2 days before ovulation), and their cutoff values were determined as described below. The patients had normal menstrual cycles (26–35 days) and were 23–44 years old. They were nonsmokers and free from major medical illnesses including hypertension. Women were excluded if they had myoma, adenomyosis, or congenital uterine anomaly or had chronic use of any medication including nonsteroidal anti-inflammatory agents.

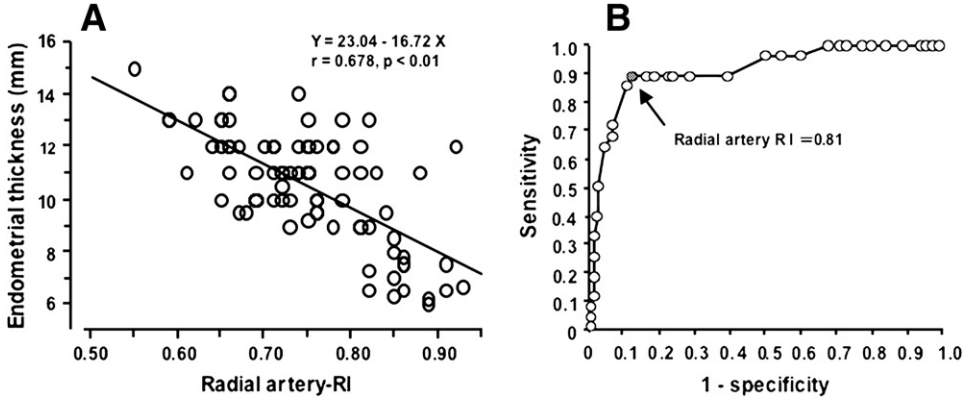
After a longitudinal view of the uterus was obtained, the thickness of the endometrium was measured at the maximal distance between each myometrial/endometrial interface using vaginal ultrasound. The cutoff value of endometrial thickness between normal and thin endometrium was defined as 8 mm based on our IVF-ET data, as reported elsewhere (5).

Blood flow impedance of uterine radial arteries was evaluated with the use of a computerized vaginal ultrasound with an integrated pulsed Doppler vaginal scanner (Aloka, Tokyo, Japan) and assessed as RI, as reported elsewhere (5, 19). The RA blood flow pattern was determined by demonstrating pulsatile color signals in the myometrium. After confirming that waveforms were continuous, an average of three to five cardiac cycles was selected for calculation of the RI. The mean of the two points of RA-RI was used for statistical analyses. Since the interobserver coefficient of variation for Doppler flow measurements in the present study was less than 10%, which is consistent with the report by Ziegler et al. (20), the Doppler flow measurements were judged to be reproducible.

There was a significant negative correlation between endometrial thickness and RA-RI, which were measured in the late follicular phase (1–2 days before ovulation; Fig. 1A). Receiver operating characteristic curve (ROC) analysis was

FIGURE 1

Correlation between blood flow impedance of uterine radial arteries and endometrial thickness. (**A**) Correlation between uterine RA-RI and endometrial thickness (n = 66). (**B**) ROC curve analysis. RA-RI and endometrial thickness were measured for infertility patients in the late follicular phase (1–2 days before ovulation). Endometrial thickness was significantly and negatively correlated with RA-RI (single regression analysis). ROC curve analysis was performed to determine the cutoff value of the RA-RI providing the best values of sensitivity and specificity for determination of normal and thin endometrium. The cutoff value of 0.81 provided the best combination, with 89.3% sensitivity and 87.6% specificity to discriminate between normal and thin endometrium.



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