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Acute efficacy of a sublingual dose of nifedipine on uterine arterial blood flow: preliminary data in prematurely menopausal women

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KEYWORDS: calcium blocker; Doppler; early menopause; embryonic implantation; miscarriage; nifedipine; uterine vascularization

ABSTRACT

Objectives *To determine whether the calcium blocker nifedipine alters Doppler velocimetry and impedance parameters in the uterine artery in prematurely menopausal women.*

Methods *Uterine artery Doppler examinations were performed transvaginally in seventeen prematurely menopausal women without the use of calcium blocker (T_0). Following a 10-mg sublingual dose of nifedipine patients were subsequently rescanned at successive time intervals ($T_{25} = 25$, $T_{40} = 40$, $T_{60} = 60$ min). PI (normalized (NPI) for heart rate) and maximum, minimum and average velocities of the uterine artery were recorded and waveforms were qualitatively assessed using Goswamy and Steptoe's waveform classification.*

Results *Quantitative analysis showed a significant decrease in NPI at T_{25} in the right and left uterine arteries (T_0: PI = 2.95 and 3.01; T_{25}: PI = 1.52 and 1.52, respectively; $P < 0.001$) and until the end of the experiment. Minimum and average blood flow velocities increased strongly ($P < 0.001$) whereas the maximum velocities did not change significantly ($P = 0.12$). Qualitative analysis revealed more conspicuous results: eight subjects presented 'abnormal' spectra: one was type A (absence of protodiastole), three were type B (absence of telediastole) and four were type O (no diastolic blood flow); all of them recovered type C waveforms (normal spectrum) during the hour following nifedipine administration.*

Conclusions *Nifedipine induces a reversible decrease in NPI and an increase in blood flow velocities in the uterine artery in prematurely menopausal women. These results suggest that nifedipine is a potent uterine arterial vasodilator. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Sonographic assessment of uterine receptivity during *in-vitro* fertilization (IVF) cycles has been studied widely. Most reports have dealt with endometrial parameters, uterine contractions and/or uterine vascularization. Friedler's meta-analysis showed that there is no significant difference in endometrial thickness between conceptional and non-conceptional IVF cycles[1] and endometrial thickness has only a negative predictive value in that very few pregnancies have been reported in cases with an endometrial thickness ≤ 6 mm[2–4]. Only descriptive studies on uterine contractions have been reported so far. A proper analysis requires adapted fitting (specific computerized system), making systematic deployment impossible and non-reproducible[5–8].

Doppler measurements during the menstrual cycle show changes in pulsatility index (PI). The decrease in PI observed during the luteal phase reflects the increase in blood flow and the endometrial neovascularization necessary for embryo implantation. Estradiol is the main mediator of this neovascularization process[9–12]. According to Goswamy and Steptoe's classification[12], when there is estrogenic deficiency the PI tends to be > 3 and uterine spectra are type O[10,11,13–17]. The value of uterine artery Doppler analysis performed on the day of embryo transfer remains controversial. Since Goswamy and Steptoe's report, equal numbers of studies have been

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published which have either shown a significant difference in the PI between conceptional and non-conceptional cycles or have failed to demonstrate it[14,18–20]. However, when the PI > 3.3 and/or there is absence of diastolic blood flow in the uterine arteries the number of pregnancies reported is very low and miscarriage rates are high[2,19–21].

There have been numerous attempts to enhance uterine vascularization during IVF cycles. Studies on the effects of low-dose aspirin, nitric oxide donors (NODs) and L-arginine have been reported and have shown mixed results[22–30]. Aspirin has been the focus of many studies since the initial report of Wada *et al.* which showed a significant improvement in pregnancy rates following stimulation cycles for frozen embryo transfer by low-dose aspirin administration in cases of poor vascularization[28]. Rubinstein *et al.* also reported an improvement in IVF biological and ultrasound parameters[29]. According to Urman *et al.*, on the other hand, administration of low-dose aspirin did not improve implantation or pregnancy rates among a non-selected group of couples undertaking intracytoplasmic sperm injection (ICSI)[30].

NODs result in a reversible increase in uterine blood flow and in a decrease of the uterine artery PI. However, NOD trials in reproductive medicine have proved disappointing. The randomized double-blind study by Ohl *et al.* of 138 IVF cycles found neither a decrease in mean PI nor an improvement in pregnancy rates[23]. This failure of aspirin and NODs (such as sildenafil) may be due to their mode of action. Aspirin has antithrombosis properties which are important after implantation, but the impact at the time of implantation itself remains unproven. Its vasodilator properties, which could be useful for IVF, are slight. The vasodilatory effect of NODs is more pronounced in veins than in arteries[31,32]. The antianginal effect of the organic nitrates is essentially induced by the dilation of the venous vasculature, which decreases cardiac preload. High nitroglycerin concentrations are necessary to reduce afterload by decreasing peripheral arterial resistances[33]. Furthermore, the comparison of the effects of nifedipine and nitroglycerin on coronary blood flow using intracoronary Doppler catheters has shown that nifedipine reduces diastolic coronary vascular resistance whereas nitroglycerin increases it[32]. Thus, the fact that nitrates are not potent arterial vasodilators may account for the contradictory findings between their impact on uterine flow on the one hand and the lack of improvement in IVF results on the other[22–26].

Nifedipine is a slow calcium channel blocker that acts directly on the arterial wall to produce a powerful reversible vasodilation effect. This accounts for its hypotensive and antianginal properties. There have been no reports dealing with the effect of nifedipine on uterine arteries in reproductive medicine. The aim of this study was to assess the effects of this calcium blocker on uterine arterial blood flow parameters in prematurely menopausal women with abnormal uterine perfusion.

METHODS

Seventeen patients from our oocyte donation program were contacted for the study. After informed written consent, they were asked to stop hormone replacement therapy, so that no hormonal influence would be added to that of nifedipine. Estradiol was assayed on the day of the ultrasound and Doppler measurements. The study did not require local ethics committee approval, since the reproductive medicine department has French Health Ministry authorization for studies without direct individual benefit.

On the day of the ultrasound study, after half an hour's rest, initial blood pressure (BP), heart rate (HR) and right and then left uterine artery Doppler measurements were recorded. The patients were then administered a 10-mg nifedipine tablet sublingually (T_0). The same parameters were again measured at various post-administration times ($T_{25} = 25$ min, $T_{40} = 40$ min, and $T_{60} = 60$ min).

A transvaginal sonographic examination was performed using a General Electrics (General Electrics Logic 500 Pro Series, Milwaukee, WI, USA) ultrasound machine equipped with a 7-MHz color Doppler vaginal probe. Right and left uterine arteries were located by means of a transverse section through the uterine isthmus. After activating color mode, the Doppler gate was positioned on the uterine artery. Three consecutive waveforms recorded from the right and then from the left uterine artery were analyzed. The results obtained from the three waveforms were averaged to obtain one value for each artery. PI, maximum velocity (Vmax), minimum velocity (Vmin) and average velocity (Va) were calculated automatically using the ultrasound system's software. Mean values are presented.

As reported by Ochi *et al.*, HR and uterine artery PI are inversely correlated; to correct for the influence of HR on the uterine artery PI we normalized PI for HR using the following formula derived from previous studies[34,35]: normalized PI (NPI) $= 0.693/(0.895 - 0.00241 \times \mathrm{HR}) \times \mathrm{PI}$.

We used the descriptive uterine spectrum analysis of Goswamy and Steptoe[12]: type O spectrum = absence of diastolic flow; type A = absence of protodiastole; type B = absence of telediastole; type C = continuous diastolic flow (normal).

Statistical analysis (analysis of variance (ANOVA) of the various parameters over time) was performed using the SPSS package (version 11.5 for Windows, 2003, SPSS Inc., Chicago, IL, USA). The significance level was set at 0.05.

RESULTS

Three of the 17 prematurely menopausal patients had Turner's syndrome and fourteen idiopathic premature ovarian failure with secondary hypergonadotrophic amenorrhea. The mean age of the patients at the time of

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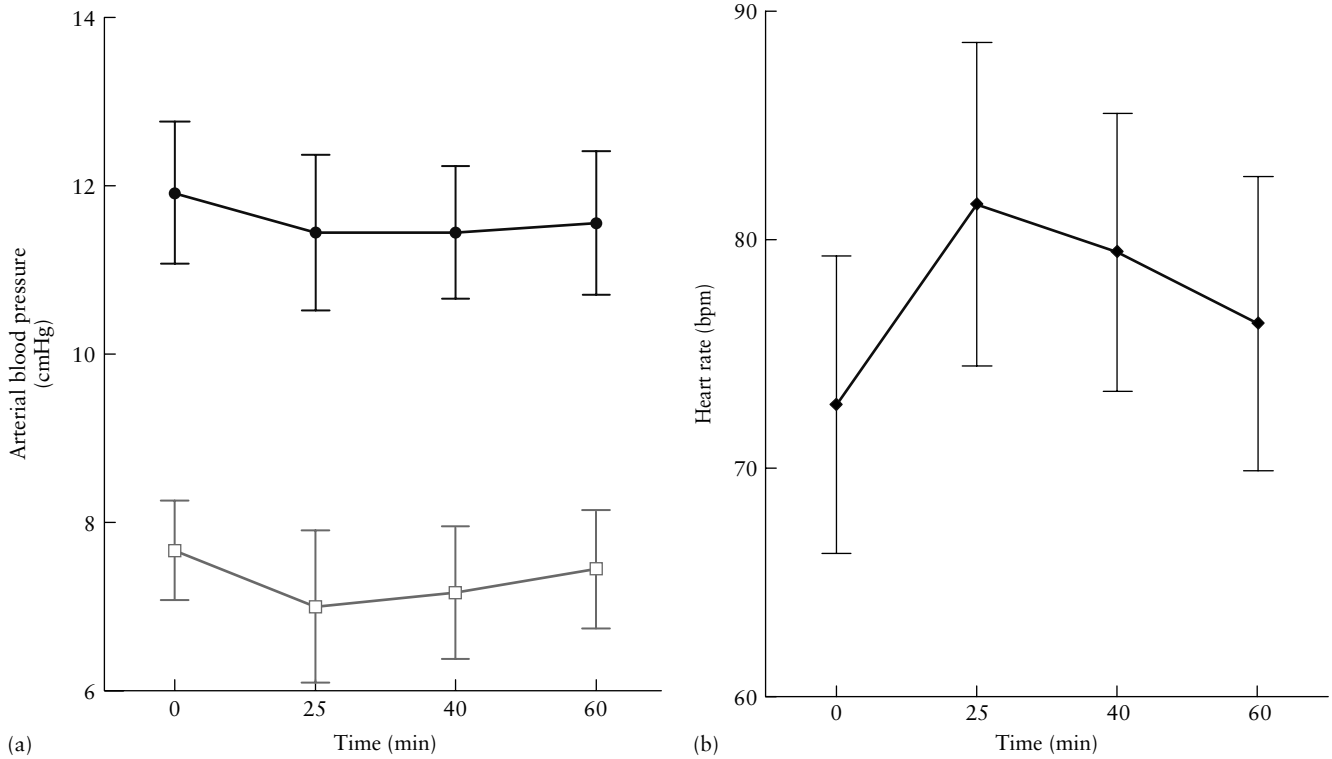


Figure 1 Mean systolic (●) and diastolic (□) blood pressure (a) and heart rate (b) plotted against time. 10 mg nifedipine was administered sublingually at 0 min.

the study was 30.1 (range, 24–39) years and the median time since the onset of menopause was 8 (range, 1.5–19) years. The median time since suspension of estrogenic supplementation treatment was 45 (range, 22–365) days. The median estradiol concentration was 0 (unmeasurable) (range, 0–355) pmol/L. No side effects were recorded except a facial flush in three cases (17.6%). Endometrial thickness did not exceed 3.5 mm in any patient.

Figure 1 shows the variations in minimum and maximum arterial BP (Figure 1a) and HR (Figure 1b). No significant variation in BP was found, whereas the rise in HR between T_0 (73.4) and T_{25} (81.7) and the decrease recorded at T_{40} and T_{60} were significant ($P < 0.001$, ANOVA).

Figure 2 shows changes in the right and left uterine NPIs after nifedipine administration. The NPI was 2.95 in the right artery and 3.01 in the left artery at T_0. At T_{25}, a significant fall of nearly 50% in NPI was observed in both arteries (NPI = 1.52 at T_{25} in both arteries, $P < 0.001$, ANOVA). It was then observed to increase progressively, non-significantly by T_{40} but significantly by T_{60} in both uterine arteries.

We also observed an increase in all arterial blood flow velocities between T_0 and T_{25}. This increase was significant for Vmin (2.85 cm/s at T_0 and 8.76 cm/s at T_{25} in the right uterine artery; 3.33 cm/s at T_0 and 9.27 cm/s at T_{25} in the left uterine artery; $P < 0.001$, ANOVA) and for Va (8.26 cm/s at T_0 and 15.66 cm/s at T_{25} in the right uterine artery; 9.43 cm/s at T_0 and 16.45 cm/s at T_{25} in the left uterine artery; $P < 0.001$, ANOVA), but not for Vmax (27.6 cm/s at T_0 and 32.52 cm/s at T_{25} in the right uterine artery; 29.09 cm/s at T_0 and 34.44 cm/s at T_{25} in the left uterine artery; $P > 0.05$ in both arteries). All the velocities then decreased slowly and significantly ($P < 0.05$, ANOVA) at T_{40} and T_{60}, without reaching the initial values.

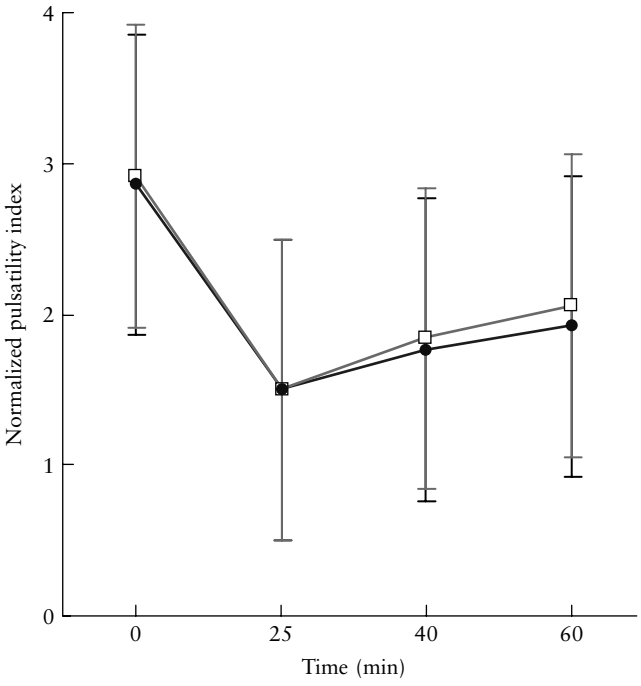


Figure 2 Mean normalized pulsatility index for right (●) and left (□) uterine arteries plotted against time. 10 mg nifedipine was administered sublingually at 0 min.

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Table 1 shows the spectrum analysis findings. All uterine artery spectra had normalized between T_{25} and T_{40}, including eight type O spectra (no diastolic blood flow at T_0). The one spectrum which had not altogether normalized by T_{25} did so by T_{40} (i.e., delayed complete response). Thus, all uterine spectra had normalized between T_{25} and T_{40}. At T_{60}, only two spectra (5.9%) had become pathological again in one patient. Figure 3 shows that nifedipine enables diastolic blood flow to be restored in case of initially weak or absent diastolic perfusion.

DISCUSSION

Since the first report by Goswamy *et al.*[18], the role of uterine artery flow velocity waveforms in the assessment of uterine receptivity has been addressed by numerous

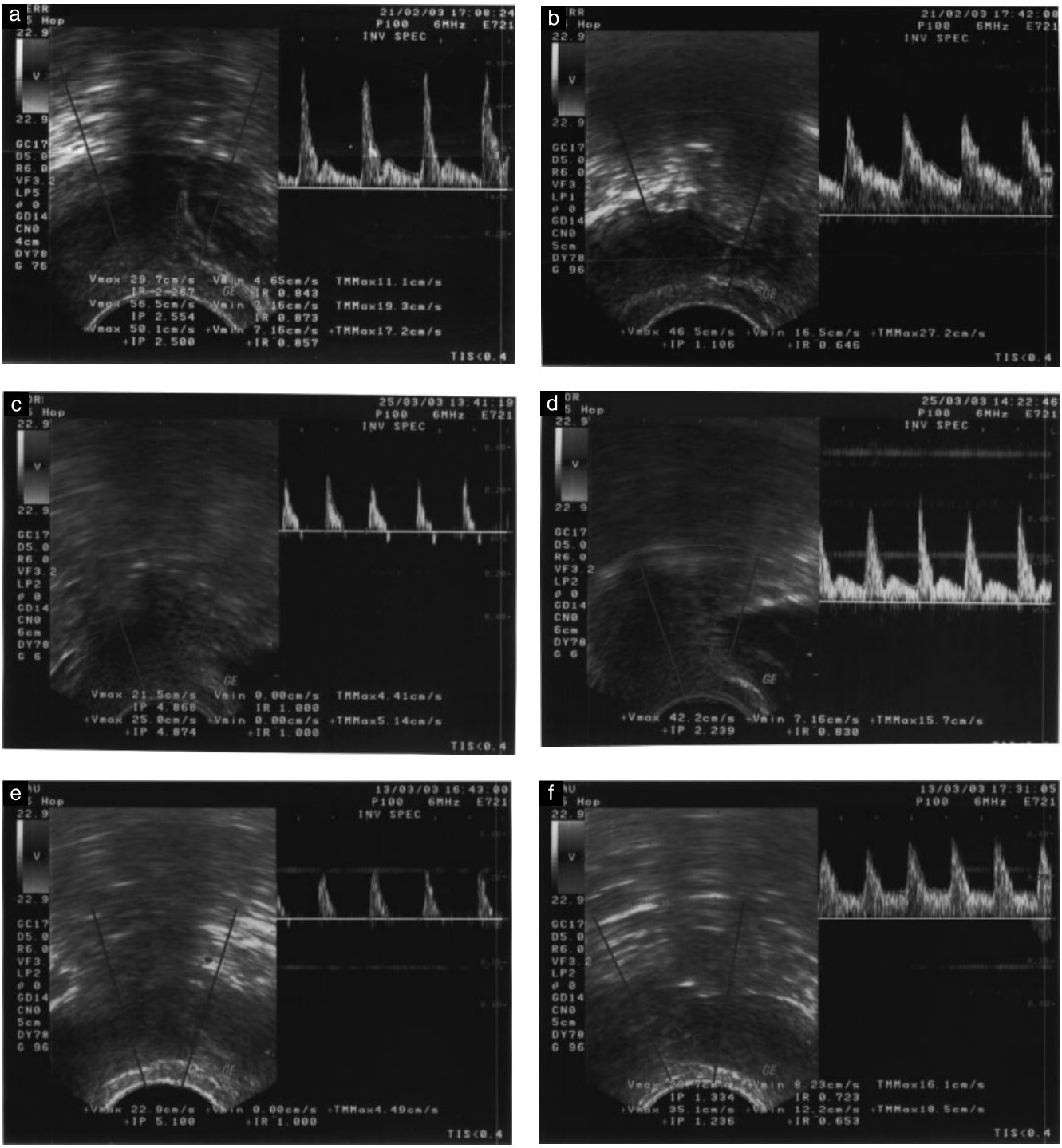


Figure 3 Uterine artery spectra in three patients. The initial pulsatility index (PI) (T_0) was around 2.5 in the first patient (a). Twenty-five min (T_{25}) after sublingual administration of 10 mg nifedipine, the PI was around 1.1 (b). In the other cases, initial diastolic blood flows were absent before treatment (T_0) ((c) and (e)). Twenty-five min (T_{25}) after sublingual administration of 10 mg nifedipine, the patients recovered a normal blood flow spectrum ((d) and (f)).

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Table 1 Changes in uterine artery spectra during the procedure

Spectrum type (*Goswamy and Steptoe's classification*[12])	n *(%)*			
	T_0	T_{25}	T_{40}	T_{60}
Type O: absence of diastolic flow	8 (23.5)	0	0	2 (5.9)
Type A: absence of protodiastole	2 (5.9)	1 (2.9)	0	0
Type B: absence of telediastole	5 (14.7)	0	2 (5.9)	0
Type C: continuous diastolic flow (normal)	19 (55.9)	33 (97.1)	32 (94.1)	32 (94.1)

T_0 is the time of nifedipine administration, and T_{25}, T_{40} and T_{60} are 25 min, 40 min and 60 min after its administration.

studies. The results of uterine artery Doppler during IVF cycles remain controversial. All studies, however, have reported significantly reduced pregnancy rates in cases with PI $\geq$ 3.3 or a type O spectrum[2,19–21]. Moreover, it has been reported that patients with recurrent spontaneous miscarriages had a significantly higher PI than did patients with normal pregnancies[36,37].

Nifedipine is a powerful arterial vasodilator used mainly for its hypotensive and antianginal properties. Its use in obstetrics has been reported in pregnancy-induced hypertension and tocolysis[38–42].

The effects of 10-mg nifedipine on uterine blood flow in pregnancy are contradictory. Veille *et al*. found no change in uterine blood flow in goats[43]. In humans, Pirhonen *et al*. observed a significant decrease of the uterine artery systolic/diastolic ratio (S/D)[44,45] whilst Thaler *et al*. recorded no significant change in S/D ratio in nine patients compared with a matched, placebo-treated group of seven patients[46]. In all instances, improving uterine blood flow appears to be difficult to achieve during pregnancy. Hormonal changes combined with the intensive release of vasodilation mediators during pregnancy, result naturally in the optimization of uterine blood flow.

In the present study, sublingual nifedipine administration led to a significant increase in HR, while arterial BP remained stable. At the same time, NPI decreased significantly in both uterine arteries. Since PI had been corrected for HR (NPI) we conclude that the decrease in NPI was due mainly to the potent vasodilatory effect of nifedipine. The consequence of this vasodilation at spectrum level was the normalization of 100% of the uterine spectra by T_{40}.

Our study set out to assess the impact of a selective arterial vasodilator on uterine blood flow in cases of poor perfusion. Nifedipine induced a reversible decrease in PI and an increase in blood flow velocities in our prematurely menopausal women. Because there seems to be a relationship between blood flow and PI (weak negative correlation) and between blood flow and blood flow velocities (positive correlation), our results suggest that uterine blood flow increases after nifedipine administration[47–49]. It is still too soon to affirm the usefulness of nifedipine in reproductive medicine, but this preliminary study paves the way for further work on improvement of uterine receptivity.

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