Endometrial perfusion across the normal human menstrual cycle assessed by laser Doppler fluxmetry

B.J.Gannon1,3, C.J.Carati1 and C.J.Verco2

1Department of Anatomy and Histology, School of Medicine, Flinders University and 2Department of Obstetrics and Gynaecology, Flinders Medical Centre, GPO Box 2100, Adelaide, South Australia 5001, Australia
3To whom correspondence should be addressed

This study investigated variations in microvascular perfusion of human endometrium across the menstrual cycle, using a laser Doppler technique to assess red blood cell (RBC) flux. Endometrial RBC flux was monitored by laser Doppler fluxmetry via a fibre optic probe inserted transvaginally into the uteri of 19 conscious normal volunteer women, on four occasions at weekly intervals over one menstrual cycle. Regional variation in RBC flux was investigated in 16 surgical patients under general anaesthesia and in five excised uteri. Endometrial perfusion exhibited short-term temporal variations consistent with the cardiac cycle and often also showed vasomotion (5–12 cycles/min). Mean endometrial perfusion differed between phases of the menstrual cycle in conscious women, being highest during early proliferative and early follicular phases. There were no significant regional differences in local mean endometrial perfusion in anaesthetized patients. No evidence of endometrial ischaemia/reperfusion episodes was found in any subject using this technique. This study provides benchmark data of variations in RBC flux per unit volume of tissue in the luminal ~1 mm of endometrium, across the normal human menstrual cycle. Flux values were highest at times associated with endometrial growth and preparation for implantation, indicating that RBC flux may be a useful parameter for assessment of endometrial physiology.

Key words: endometrium/laser Doppler fluxmetry/menstrual cycle/menstruation/uterine perfusion

Introduction

A number of studies have reported differences in uterine blood flow or uterine artery impedance between the different phases of the human menstrual cycle (e.g. Fraser et al., 1987; Goswamy and Steptoe, 1988), or after exogenously applied sex hormones (de Ziegler et al., 1991; Hilliard et al., 1992; Tekay et al., 1995). However, relatively little is known about perfusion patterns of the endometrium itself. For example, it has been suggested that endometrial bleeding and tissue sloughing at menstruation occur as a consequence of episodes of endometrial ischaemia and reperfusion (Speroff et al., 1994), but there is little definitive evidence for this. The measurement of human endometrial perfusion has greater significance than simple physiological interest. For example, an increased probability of successful pregnancy following embryo transfer is reported in women in whom endometrial perfusion is presumed to be higher (Steer et al., 1992, 1995).

Previous measurements of human endometrial perfusion have utilized either clearance of intraluminally or intramurally injected 133Xe (e.g. Fraser et al., 1987), or monitored the clearance of locally applied heat from the endometrium (thermistor anemometry; Akerlund et al., 1975). Clearance of radioactive Xenon gas from the uterine lumen necessarily involves averaging endometrial blood flow over the entire uterine lumen, over several minutes; hence, this method is poorly discriminant both spatially and temporally. Thermistor anemometry has better spatial and temporal resolution than radiolabel clearance techniques, but has inherent methodological problems (Prill, 1963). Recently, several authors have reported changes in endometrial perfusion using colour Doppler ultrasonography of intra-endometrial arteries. Changes in perfusion are reported around the time of ovulation (Kupesic and Kurjak, 1993) and throughout the cycle (Steer et al., 1990; Kurjak and Kupesic, 1995; Achiron et al., 1995a), and in postmenopausal endometrium (Achiron et al., 1995a,b). However, whether this method can identify flow in individual intraendometrial spiral arterioles requires verification.

Laser Doppler fluxmetry is a physiologically non-invasive technique for continuous monitoring of the flux of red blood cells (RBC) through a relatively confined tissue volume (~1 mm diameter sphere; Johannson et al., 1991; Mayrovits, 1992) per unit time, i.e. an index of local tissue haematocrit; an algorithm utilizing these two parameters provides an index of the number of RBCs transiting the monitored volume (~1 mm diameter sphere; Johannson et al., 1991; Mayrovits, 1992) per unit time, i.e. an index of local tissue perfusion. This method has sufficient temporal resolution to distinguish variations in local tissue perfusion associated with cardiac and respiratory cycles (Kvernebo et al., 1986; Sundseth et al., 1993). To our knowledge, laser Doppler measurement of endometrial perfusion has not been reported previously for any mammal. We have used this method for the measurement of endometrial perfusion across the phases of the human menstrual cycle in conscious volunteer women with normal

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Materials and methods

Institutional Research and Ethics Committee approval was sought and obtained from Modbury Hospital, South Australia, where these studies were performed. Informed, witnessed consent was obtained in writing for all subjects.

Subjects

Laser Doppler measurements of endometrial perfusion were made in two groups of women: conscious volunteers (n = 19) and operative patients (n = 16).

Conscious volunteers were women aged 21–46 years old who provided a gynaecological and menstrual history, including the date of the last menstrual period (LMP). Endometrial perfusion measurements were made in each volunteer once per week over 4 weeks (usually of one cycle) without anaesthesia or analgesia. All measurements were made in the morning to avoid possible variation due to circadian rhythms in uterine blood flow (Zaidi et al., 1995a,b).

The volunteer was supine on an examination couch with hips and knees flexed as for a cervical smear; the vestibule and vagina were cleansed with antiseptic soaked swabs (povidone iodine, Betadine; Faulding Pharmaceuticals, Salisbury, SA, Australia). The vagina was gently dilated, and the tip of the flexible fibro-optic laser Doppler probe (2.1 mm diameter, Vasamedics PR-436; Vasamedics, St Paul, MN, USA) was placed at the external cervical os with plain forceps; by the application of gentle pressure along the probe shaft, the probe tip was passed without difficulty through the cervix and advanced into the uterus to 5 cm from the external cervical os (this distance was chosen from preliminary studies of regional differences in perfusion measurements in anaesthetized patients, see below). Brief measurements (15–30 s) were made at several adjacent sites by minor advancing/withdrawal/rotation of the probe until three consecutive, stable measurements within 20% of each other were made; typically this occurred within five measurements. The last of these sites was used for extended monitoring over 10–15 min to assess temporal variations in local endometrial perfusion. This time was a reasonable limit in terms of subject comfort and compliance. Flux measurements did not appear to be adversely affected by relocation of the probe.

Operative patients were women aged 19–39 years, without proven pathology of the uterus, who agreed to participate in this study. These patients were undergoing laparoscopy/laparotomy at Modbury Hospital (for e.g. endometriosis, unexplained pelvic pain, tubal ligation or investigations). The gynaecological history, including the LMP (by self-report) was noted. Endometrial perfusion measurements were undertaken immediately after induction of general anaesthesia, but prior to surgery. General anaesthesia was by a variety of clinically-acceptable techniques. The gynaecological history, including the LMP was recorded by self-report. The measurements of endometrial blood flow in conscious volunteers (see above); it was carefully advanced to the cervix, this location being indicated by resistance to further probe advancement. Endometrial perfusion was measured at this site for approximately 10 min; the probe was then withdrawn by 1–2 cm stages, with several further measurements of ~10 min being made at sites between the fundus and the external cervical os.

An additional five patients, undergoing elective hysterectomy, allowed measurement of ‘biological zero’ laser Doppler measurements (i.e. measurements of the same tissue without any blood flow occurring; Colantuoni et al., 1993), immediately following removal of the uterus. Endometrial perfusion (1–2 min duration, n = 31) was measured at each of several sites between the fundus and the external cervical os; these measurements commenced within 5 min of organ excision and were completed within a further 10 min.

Equipment

A TSI Laserflo BPM 403A laser Doppler instrument (Vasamedics; λ = 780 ± 20 nm, 2 mW at probe tip) was equipped with a thin flexible endoscope probe measuring at 90° to the probe axis (Vasamedics PR-436; 2 m long × 2.1 mm diameter). The diameter of this probe is less than that of the standard Micropipelle endometrial suction biopsy device (3.1 mm diameter; Laboratoire CCD, Paris, France), which is used in unanaesthetized women in routine clinical gynaecological practice. The probe was sterilized by immersion in a 2% glutaraldehyde solution (Cidex; Johnson and Johnson Medical, Australia) for 10 min, then rinsed in sterile water prior to each use. Indelible black marks, 1 cm apart on the external white polymer casing of the probe, allowed ready estimation of the extent of probe advancement/withdrawal through the cervix. ‘Flow’ measurements from the instrument (averaging time 0.1 s) were charted on the instrument’s built-in chart recorder (100 mm/min; sensitivity ×4), and recorded on an IBM-XT clone computer (ASI, Taiwan) via a CODAS Analog to Digital data recording system (Dataq Corp, Akron, Ohio, USA) at 10 samples/s. All measurements reported here were made using the same fibre optic probe; values are reported as laser Doppler flow ‘units’ (mlg/min/100 g tissue). These are uncalibrated instrument units, which the instrument manufacturer indicates are equivalent to local tissue blood flow in ml/min/100 g tissue. The instrument recorded 25 ± 1 (mean ± SE) TSI ‘units’ (gain at ×1) when the probe was placed in a vial of colloidal motility standard (Periflux PF-100; Perimed AB, Stockholm, Sweden; this standard provided a constant reflectance and Doppler shift, based on Brownian motion of the suspension, to allow calibration of laser Doppler flowmeters).

Statistical analysis

Average flux values for the sampling period were obtained from the Codas software, and verified by comparison with the TSI chart recorder output. This output was visually inspected for clearly discernible peaks of 12 cycles per min or less (Figure 1), which were interpreted as vasomotion, and are reported as cycles/min. Data are presented as mean ± SE; data analysis was by analysis of variance (ANOVA) and post hoc testing, as appropriate.

The measurements of endometrial blood flow in conscious volunteers were grouped according to the phases of the menstrual cycle used by Fraser et al. (1987), and the results for each phase were averaged (menses phase (days 1–5), early (days 6–9) and late (days 10–12) follicular phase, ovulatory phase (days 13–16) and early (days 17–22) and late (days 23–28) secretory phases). However, because of the small variation in lengths of the menstrual cycles reported by our normal volunteers, we chose not to correct the cycle day of measurement to an idealized 28 day cycle.
Figure 1. TSI laser Doppler perfusion records of endometrial perfusion measured as laser Doppler flux units (LDFU) of a 32 year old conscious volunteer ‘BL’, who typically menstruated for 5 days of a 28 day cycle. The upper trace shows regular fluctuations in local perfusion (‘vasomotion’, 4.9 cycles/min), three of which are expanded in the lower trace. Vertical scale is the same for both traces. Arrows indicate flow peaks.

Results

Conscious volunteers

The placing of the measuring probe was routinely accomplished in all volunteers without significant discomfort, bleeding, or other evidence of tissue trauma; uterine perforation or other complication did not occur in any subject. Measurements of endometrial flux were made at one site only, situated 5 cm beyond the external cervical os (n = 19 subjects; 67 measurements), for each of 4 consecutive weeks, usually of a single menstrual cycle. Menstrual cycles ranged from 23 to 30 days (27.5 ± 0.4) by self report, and menstruation was of 2–7 days duration (4.8 ± 0.3). This group comprised six nullipara, three uni- and 10 multi-parous women.

On inspection, the RBC flux records of volunteers typically showed cyclic variations at two basic frequencies, one consistent with heart rate, and often another slower frequency (usually 5–8 cycles/min; range 1.2–12 cycles/min) more variable amplitude cycle, presumed to be vasomotion (Figures 1 and 2). The frequency of the vasomotion was not significantly different over the phases of the menstrual cycle (Figure 3; ANOVA, F_{5.56} = 0.46, P = 0.8). No episodes of transient ischaemia of the endometrium were observed in the 67 records from conscious volunteers, including 13 records obtained during menstruation.

Mean RBC flux was influenced by phase of cycle (ANOVA, F_{5.61} = 7.24, P <0.001), being highest in the early follicular and early secretory phases (Figure 4). The mean values for the early follicular and early secretory phases were significantly different from those for all other phases, which were not different from each other (Bonferroni test).

Anaesthetized patients

Laser Doppler fluxmetry records of perfusion of individual endometrial sites in anaesthetized patients (n = 16 subjects; 57 measurements) revealed temporal variations similar to those observed in records from conscious volunteers. Regional mean endometrial RBC flux did not vary significantly within the uterus between fundus, body, internal and external cervical os in surgical patients; however, there was a non-significant trend for the highest flux values to be recorded at the fundus, and
Human endometrial perfusion

Biological zero measurements

Laser Doppler measurements undertaken in five freshly excised uteri (in which there could be no blood flow), showed low flux values of 1.5–12 units; these ‘biological zero’ measurements in the freshly excised, non-perfused organ revealed a similar overall trend to that seen in the perfused organ in vivo. That is, the biological zero value was higher at the fundus, and external cervical os, and lower at the internal cervical os than in the body of the uterus.

Discussion

This study provides baseline measurements of local endometrial perfusion across the menstrual cycle in normal women, using transvaginal laser Doppler fluxmetry. What is actually measured by laser Doppler is not ‘blood flow’, but rather the relation to phase of menstrual cycle for 19 conscious volunteer number of RBC making a transit across the small volume of tissue monitored by the fibre-optic probe; the derived value, RBC flux, is an index of local tissue perfusion (Nilsson et al., 1980). As reported for other tissues, our RBC flux records usually revealed two basic cyclic variations, one consistent with cardiac cycle and a slower cyclic variation, often of greater amplitude, which was presumed to be due to vasomotion (Kvernebo et al., 1986; Sundset et al., 1993). We cannot exclude the possibility that this slower cyclic variation was caused by relative movement of the probe tip with respect to the tissue, due to slight subject movement, or to muscular contractions of the uterus (Cibils, 1967; Moawad and Bengtsson, 1967; de Vries et al., 1990), contractions of the sub-endometrial myometrium (Lyons et al., 1991), or to peristalsis-like movements within the endometrium itself (Abramowicz and Archer, 1990). However, rhythmic vasomotion has been directly observed in the guinea-pig uterus by Markee (1932) and was recorded by thermistor anemometry in human endometrium by Prill (1963).

We observed low ‘biological zero’ flux measurements (Colantuoni et al., 1993) in excised uteri. The regional trend in magnitude of these ‘zero’ measurements mirrored those in the intact uterus in situ in anaesthetized patients (highest at fundus, lowest at internal cervical os). We chose not to correct our laser Doppler records for biological zero, because we had only five excised uteri available for measurement, which did not represent all stages of the menstrual cycle. The significance of low laser Doppler flux measurements in excised non-perfused human uteri is yet to be determined. These measurements may represent arterial myogenic vasomotion reported in other non-perfused organs (Colantuoni et al., 1993) or continuing myometrial smooth muscle activity of the excised uterus, resulting in the relative movement of the probe with respect to red cells within the endometrium.

In our recordings of endometrial RBC flux, the tissue volume sampled at any one time is likely to have been quite small (a superficial sphere of ~1 mm diameter; Johansson et al., 1991; Mayrovitz, 1992). Thus, this recording may not be representative of the entire endometrium, or even of the adjacent endometrial tissue. It is clear, however, that laser Doppler recording of local RBC flux, with its inherently good spatial and temporal resolution, could identify focal or...
transitory events which otherwise would be averaged out in measurements of $^{133}$Xe gas clearance from the uterine cavity, as was used to estimate blood flow through the entire endometrium (Fraser et al., 1987). In comparing our results with those of previous workers, three points emerge. Firstly, the laser Doppler RBC flux values reported here (mL/min/100 g; uncalibrated units) are quite similar to the absolute values of human endometrial blood flow (mL/min/100 g) reported by Fraser et al. (1987) from $^{133}$Xe gas clearance, and by Zhang et al. (1995) who used a hydrogen clearance technique to measure rat endometrial blood flow. Thus, the statement by the manufacturer of the laser Doppler unit used in this study (Vasamedics) that the ‘flow’ units measured represent blood flow in mL/min/100 g tissue appears to be reasonably applicable to the endometrium, even though the methods described above measure blood flow by fundamentally different methods. Laser Doppler fluxmetry measures the passage of red cells through a sphere of ~1 mm diameter, whereas precisely how the clearance of radioactive $^{133}$Xe gas from the uterine cavity occurs via blood is unclear (i.e. is this tracer principally transported by carriage in plasma, or in red cells, or similarly in both?). We consider that the physical bases of the other endometrial ‘flow’ measurements by Markee (1940; RBC velocity by eye) and Prill (1963; clearance of applied heat) cannot accurately quantify local blood flow, and hence are not comparable with our results.

Secondly, other studies which directly measured endometrial blood flow report changes in endometrial perfusion across the menstrual cycle which differ from the patterns found in this study. Fraser et al. (1987) reported highest endometrial blood flows around days 10–12 and days 21–26 of the cycle; in the current study, we found two RBC flux peak values at slightly earlier times in the cycle (around days 6–9 and days 17–22). A possible explanation of this discrepancy may lie in differences between the two methods in terms of sensitivity to the changing tissue parameters of epithelial thickness, microvessel density and perhaps microvessel distance from the uterine lumen, since laser Doppler RBC fluxmetry and $^{133}$Xe gas clearance monitor different aspects of endometrial perfusion. The pattern of RBC flux changes in our study does not correspond to that reported from thermistor anemometry studies by Prill and Götz (1961); however, their results are not directly comparable to those reported here, since their heat clearance technique measures plasma flow as well as RBC flux. Their measurement method, thermistor anemometry, is now considered a primitive technique (Akerlund, 1995). It exhibits a variable calibration from day to day (Prill, 1963), and involves local heating of the monitored tissue region by up to 4–5°C.

Thirdly, from our assessment of regional variation in anaesthetized and conscious subjects, perfusion monitoring by laser Doppler from quite small sites within the endometrium appears to be representative of perfusion throughout this tissue. This method appears to give measurements equivalent to, but more quickly and less ‘invasively’ than those for radioactive $^{133}$Xe gas clearance (Fraser et al., 1987), which averages entire endometrial perfusion over several minutes, and involves gamma radiation of the female pelvis, albeit at low dose. Thus, endometrial laser Doppler fluxmetry may be useful clinically, provided spatial and temporal variation in perfusion patterns are assessed. In more recent studies of endometrial perfusion, we assessed the spatial variation by measuring perfusion at five randomly chosen sites, using a repeated analysis of variance design; the coefficient of variation within subjects was high, but variation within treatment groups was reduced by increasing the number of sampling sites. It is worth noting that moving the probe did not significantly or consistently affect perfusion, implying that repositioning the probe is not an invasive event (unpublished observations).

There were substantial changes in mean perfusion across the menstrual cycle both for individual women (e.g. Figure 2), and for the volunteer group as a whole (Figure 4). Endometrial RBC flux peaks during the early follicular phase, when oestrogen concentrations are low but rising, and again in the early secretory phase when both oestrogen and progesterone concentrations are rising (Shaw and Roche, 1980). It is not yet clear whether the differences in local RBC flux are explicable in terms of the absolute concentrations or rate of change of, and/or the ratio between, these major reproductive hormones. It may be that, for the early follicular phase, RBC flux is highest because this phase has the highest rate of endometrial cell proliferation (Ferenczy et al., 1979) and so requires a greater tissue nourishment and hence perfusion. Endometrial oedema, characteristic of the late follicular phase (Noyes et al., 1950), may account for the lower flux values we recorded during this phase. The oedema during this phase may increase the inter-microvessel distance in the tissue and, hence, reduce the actual number of microvessels present within the volume monitored by the laser Doppler probe. A reduction in endometrial microvessel spatial density would account for a reduction in RBC flux, even if blood flow per capillary were maintained; in fact, blood flow per capillary may actually be reduced during oedema.

The high RBC flux during the early secretory phase may be explicable in terms of preparation of the endometrium for implantation. The fall in RBC flux during the late secretory phase is harder to explain. During this latter phase, the endometrium first becomes visibly oedematous and then undergoes a marked reduction in overall volume of ~50% immediately prior to menstruation (Shaw and Roche, 1980). A reduction in laser Doppler measured perfusion during the oedematous phase could be due to the increase in intercapillary spacing as tissue volume expands (see above); thus, the number of microvessels present in the monitored 1 mm diameter sphere would be reduced by oedema, and so the measured flux value should decrease, provided RBC flux per microvessel was unchanged. A reduction in endometrial capillary spatial density in the mid–late secretory phase compared to the early secretory phase has previously been reported by Hourihan et al. (1991). This is the time of maximal endometrial oedema (Johansson et al., 1987) and the time when individual endometrial capillaries are maximally dilated (Peek et al., 1992).

The substantial regression in endometrial volume just prior to menstruation should result in an increase in endometrial microvascular density and, hence, RBC flux measurement, assuming that flux per microvessel is maintained and no
microvessels are occluded at this stage. The reduced signal actually recorded at this phase must be either a result of a substantial decrease in RBC flux per microvessel, or be due to perfusion of a substantial proportion of the endometrial microvessels being shut down (Peek et al., 1992).

Endometrial thickness varies over the cycle, from ~0.5–1.0 mm postmenstrually to 3–5.5 mm premenstrually (Speroff et al., 1994). Therefore, recording of endometrial RBC flux in the superficial ~1 mm by laser Doppler fluxmetry from the uterine lumen may in fact measure different microvessel beds at different phases of the menstrual cycle. For example, immediately after the cessation of the menstrual flow, the endometrium consists of only a thin layer of endometrial functionalis tissue over the (~1.0 mm) basalis (Speroff et al., 1994). Thus, laser Doppler flux values measured from the lumen at this time may principally represent blood flow through capillaries of the endometrial basalis vascular bed, which is supplied by the straight endometrial arterioles (Schmidt-Matthiesen, 1963). Later in the cycle, as the functionalis progressively thickens over the ovulatory and secretory phases, the microvascular bed being monitored is presumably restricted to the more superficial ~1 mm of the functionalis, i.e. the region supplied by the endometrial spiral arterioles (Schmidt-Matthiesen, 1963). Indeed, since in some areas the entire endometrial thickness may be <1 mm at this time, there may be some contribution to the laser Doppler signal from the underlying myometrial microvascular bed. Thus, the actual microvascular bed being monitored from the uterine lumen by laser Doppler fluxmetry may vary over the course of the cycle; this caveat also applies to alternative methods of direct monitoring of endometrial perfusion from the uterine lumen (133Xe clearance and thermistor anemometry).

It has been suggested that endometrial shedding at menstruation in women is a consequence of focal ischaemia–reperfusion of spiral arterioles (Speroff et al., 1994). Scant evidence supporting this includes: (i) direct observations, in endometrial transplants within the anterior eye chamber in perimenstrual rhesus monkeys, of highly focal ischaemic episodes in regions supplied by individual arterioles (Markee, 1940), and (ii) the temporal coincidence of episodes of reduced endometrial blood flow with raised intrauterine pressure during uterine cramping in women with dysmenorrhoea (Hauksson et al., 1988). We found no evidence of episodes of either endometrial ischaemia or ischaemia–reperfusion, either perimenstrually or at any other stage of the cycle. Note, however, that laser Doppler fluxmetry has limited spatial resolution, and thus there is a low probability of detecting ischaemia–reperfusion if it is highly focal in nature (i.e. limited to an individual spiral arteriole while adjacent arterioles continue to flow normally), or prolonged in duration (i.e. longer than our 10 min sampling time). Thus, if endometrial ischaemia–reperfusion episodes do occur during menstruation, they are likely to be focal, and/or >10 min duration.

Recently, estimates of endometrial perfusion at different stages of the menstrual cycle (Goswamy and Steptoe, 1988; Tekay et al., 1995) have been based on pulsatility and/or resistance indices of colour Doppler ultrasound measures of uterine artery blood flow, computed over several consecutive heart beats. The uterine artery also provides a significant branch to the ipsilateral ovary (Fleischer, 1991), Fallopian tube, and upper vagina (Warwick and Williams, 1973); during the menstrual cycle, ovarian arterial blood flow indices may rise more significantly for the ovary in which the dominant follicle is developing than for the contralateral ovarian artery (Scholtes et al., 1989). Hence, the extent to which colour Doppler-derived increases in uterine artery pulsatility index during the cycle actually represent changes in blood flow to the uterus itself remains unclear, and this may explain some of the controversy in this area. In addition, the microvascular beds of the endometrium and the myometrium are essentially separate, discrete and in parallel (Ramsey, 1977; Rogers and Gannon, 1981), so that estimates of total uterine arterial blood flow do not distinguish between endometrial and myometrial vascular beds. Thus, interpreting changes in endometrial perfusion consequent upon an increase in uterine artery blood flow is not possible from measurements or indices of uterine arterial flow alone.

Recently, the ability to image (presumably individual) spiral arterioles ultrasonically within the endometrium around the time of ovulation, and to track changes in spiral arteriolar blood flow was reported (Kupesic and Kurjak, 1993, 1995; Achiron et al., 1995a,b). Given the tortuosity of individual spiral arterioles, and also the reported spacing of the luminal surface territories of each spiral arteriole as from 4 to 9 mm² (i.e. inter-arteriole spacing of 2–3 mm), it is not clear whether the signals reported from endometrial ultrasonography come from one only, or from more than one spiral arteriole. A recent series of papers from Achiron et al. (1995a,b) report changes in endometrial arterial pulsatility index from colour Doppler ultrasonography in both normal women over the reproductive cycle, and in post-menopausal women given hormone replacement therapy; the criteria they used to identify endometrial arteries (vessels located within 10 mm of the lateral endometrial border) do not appear to unequivocally establish these as endometrial spiral arterioles, as opposed to the straighter basalis arterioles (Schmidt-Matthiesen, 1963), nor do their criteria exclude the possibility that the vessels measured were subendometrial (i.e. intra-myometrial), especially in menstrual and early follicular (proliferative) phases, when the endometrium is <2 mm thick.

Determining the actual change in endometrial blood flow represented by a reduction in uterine artery pulsatility index measured over only a few consecutive cardiac cycles may also be problematic. Our laser Doppler records suggest such estimates are likely to be erroneous, since endometrial perfusion is characterized by marked cyclic temporal variation due to vasomotion. Substantially different pulsatility indices would result, depending on precisely which few consecutive heartbeats were averaged (see Figures 1 and 2); thus, it is apparent that averaging over several minutes would be required in order to minimize sampling errors.

This study has provided benchmark data on the variations in RBC flux per unit volume of tissue in superficial human endometrium across the normal human menstrual cycle. Both the delivery of oxygen and the clearance of tissue carbon dioxide are functions of the passage of red cells through a
tissue’s microvascular bed; while the precise relationship between these parameters and RBC flux requires further clarification, it seems likely that the measurements reported in this study have physiological relevance for uterine function. Laser Doppler study of local tissue perfusion (RBC flux) in other endometrial states (e.g. under the influence of exogenous hormones and in pathological conditions), currently under investigation, will assist in developing a better understanding of the significance of this parameter in normal and abnormal endometrium.

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