Menorrhagia and uterine artery blood flow

R. Hurskainen 1,2,3, J. Teperi 2, J. Paavonen 1 and B. Cacciatore 1

1 Department of Obstetrics and Gynaecology, University of Helsinki, Haartmanink 2, FIN-00290 Helsinki and 2 Health Services Research Unit, Stakes, Siltasaarenk. 18, FIN-00531 Helsinki, Finland
3 To whom correspondence should be addressed

Menorrhagia is a significant problem in women of reproductive age. In half of the cases no specific aetiology is known. Vascular factors play a role but remain poorly understood. We chose to study whether any association exists between the flow impedance of uterine arteries and the amount of menstrual blood loss. The study population consisted of 60 spontaneously menstruating 35- to 49-year-old women without endometrial hyperplasia, polyps, or submucous fibroids. The pulsatility index (PI) from uterine arteries, arcuate arteries, and radial arteries was measured by transvaginal colour Doppler. Menstrual blood loss was measured by the alkaline haematin method. A significant inverse correlation was found between uterine artery PI and the amount of menstrual blood loss, suggesting that women with lower uterine flow impedance bleed more. A regression model confirmed that this association was specific and not explained by uterine size, fibroids or any other of the 11 potential confounders included in the model. The correlation between uterine artery PI and amount of menstrual blood loss suggests that vascular factors may be involved in the pathogenesis of menorrhagia.

Key words: blood flow velocity/Doppler velocimetry/menorrhagia/pulsatility index/uterine arteries

Introduction

Menorrhagia (menstrual bleeding >80 ml per period) is one of the most common problems in gynaecology (Coulter et al., 1989). Although new diagnostic methods have improved the clinical triage of menorrhagia, approximately half of the cases show no underlying pathology (Rees, 1987). Vascular changes may play an important role, but remain poorly studied.

Studies with transvaginal sonography (TVS) coupled with colour Doppler have shown that the uterine artery pulsatility index (PI), measuring arterial flow impedance (Gosling, 1976), is higher in amenorrhoeic and climacteric than in menstruating women (De Ziegler et al., 1991). On the other hand, PI is reduced by hormone replacement therapy and the restoration of cyclic withdrawal bleeding (De Ziegler et al., 1991). Moreover, women with menorrhagia induced by an intrauterine device (IUD) have lower PI values than those without menorrhagia, with or without IUD (Momtaz et al., 1994). These data imply a possible association between uterine blood flow and menstrual blood loss (MBL).

To test this hypothesis we used transvaginal colour Doppler to measure the flow impedance of uterine arteries in pre-menopausal women referred for menorrhagia, and we compared these data with objective measurements of menstrual blood loss.

Materials and methods

After informed consent, we studied 60 spontaneously menstruating women referred for menorrhagia to the Department of Obstetrics and Gynaecology, University of Helsinki. The characteristics of the study population are presented in Table I. We excluded patients in whom endometrial polyps, hyperplasia, or submucous fibroids were diagnosed by TVS or endometrial biopsy (Pipele), as well as those who had taken hormonal preparations during the previous month, or who had an intrauterine contraceptive device. All abnormal TVS findings were confirmed by hysteroscopy or saline infusion.

Patients were scheduled for TVS at cycle days 2–8, and were instructed to collect all tampons and sanitary pads used during the next menstrual period for objective evaluation of their menstrual blood loss. MBL was measured during the subsequent menstrual period to minimize the problem of spilled blood during the ultrasound examination which normally took at least half an hour. The alkaline haematin method was used to measure the MBL (Hallberg and Nilsson, 1964). A detailed history including parity, contraceptive method, menstrual pain, regularity of cycles and smoking was obtained from all women.

A gynaecologist experienced in TVS performed all examinations with a 9.5-MHz broadband probe (ATL HDI 3000; Bothell, WA, USA). The examiner was blinded to the patients’ clinical characteristics. Uterine maximum antero-posterior diameter and width were systematically measured and fibroids over 10 mm in diameter and endometrial thickness were recorded. Colour Doppler was used for imaging the ascending uterine arteries lateral to the cervix, the arcuate arteries in the outer third of the myometrium, and the radial arteries along their course towards the endometrium. The PI was measured from representative flow velocity waveforms of each of these vessels including three cardiac cycles by the formula:

\[ \text{PI} = \frac{(A - B)}{\text{mean}} \]

where A is the peak systolic Doppler shift frequency, B is the end-diastolic shift frequency and mean is the mean maximum Doppler shift frequency over the cardiac cycle (Gosling, 1976).

All examinations were performed between 10.00 and 12.00h to reduce the effect of circadian variation in PI (Zaidi et al., 1995). The reproducibility of the pulsatility index was tested by measuring these variables in 10 patients three times at 10-min intervals. The intraobserver coefficient of variation for the measurement of PI was 5.3% in the uterine, 6.1% in the arcuate and 6.5% in the radial artery.
Menstrual pain (mean 1.50, SD 0.47, the uterine artery (mean 2.20, SD 0.51) than in the arcuate
in 35 (58%) women.
above 80 ml, objectively indicating menorrhagia, was found
FSH
5
Contraceptive method
Endometrial thickness (mm) 60 5.3 3.0–10.0
Age (years) 60 44 35–49
Table I. Characteristics of the study population
Regularity of cycles
Menstrual pain
Partner’s sterilization
No contraception
No contraception
12 20
9
0.01) or radial arteries (mean 1.24,
increase in subjects with fibroids excluded, this correlation was even
stronger (r = 0.50, P < 0.005, n = 28) (Figure 2). No correlation was found between the PI of the arcuate or radial
artery and logMBL and the other measured variables.
After accounting for the effect of all confounding variables, the
PI of the uterine artery remained a highly significant
correlate of logMBL (r = 0.97, P < 0.001). A second
other independent variable showing an association with logMBL was the size of
the uterus (r = 0.95).
Menorrhagia and uterine artery blood flow

Discussion
The present study showed a correlation between the uterine
artery PI and the amount of MBL. This association remained
highly significant after adjustment for a large number of
potential confounders. This fact strongly suggests a true
relationship between uterine vascular tone and menorrhagia.
The pathogenesis of idiopathic menorrhagia is poorly
understood. Increased uterine contractility is associated with
decreased endometrial blood flow (Hauksson et al., 1988), and
also uterine artery PI is highest on the first day of menstruation
(Sladecevicius et al., 1994) when myometrial activity is highest
(Hauksson et al., 1988). These findings indicate that reduced
basal tone or contractility decreases the compression of vessels
traversing the uterine wall, resulting in decreased resistance
to flow.
Changes in relationships between serum and local concentra-
tions of vasoactive compounds such as prostaglandins, endo-
thelins and prostacyclins may be associated with uterine flow
impedance in the endometrial vascular bed. The menstrual
blood loss is thought to be determined by the balance between
the vasoconstrictor prostaglandin F (PGF) and the vasodilators
prostaglandin E (PGE) or prostaglandin I2 (PGI2) (Smith et al.,
1981a). In menorrhagia, the endometrial uptake of arachidonic
acid is increased (Downing et al., 1983), and conversion of
exogenous arachidonic acid to PGE2 (Smith et al., 1981a) or
prostacyclin (Smith et al., 1981b) is enhanced. Both dilate
blood vessels and inhibit platelet accumulation, thus increasing
uterine bleeding. This could well lead to decreased impedance
of the uterine artery. The role of uterine endothe-
lins in uterine blood flow is also interesting. The immunocytochemical
localization of endothelin-like immunoreactivity in basal endo-
metrium suggests that these potent peptides may not only be
candidates for the endometrial vasoconstrictor, but may also
be involved in the mediation of uterine contractions and
endometrial proliferation (Cameron et al., 1991, 1995), thus
possibly interfering with the uterine blood flow.
There are also other possible mechanisms explaining the
association of the PI of uterine artery with MBL. Growth
factors stimulate angiogenesis, the growth of new blood vessels,
which follows menstruation (Findlay, 1986). Women with
menorrhagia show a significant increase in endothelial cell
proliferation, reflecting disturbed angiogenesis (Kooy et al.,
1996). Studies utilizing light microscopy have demonstrated

Results
The mean MBL was 124 ml (19–594 ml) (Figure 1). An MBL
above 80 ml, objectively indicating menorrhagia, was found
in 35 (58%) women.
Uterine PI was significantly higher in the main branch of
the uterine artery (mean 2.20, SD 0.51) than in the arcuate
(mean 1.50, SD 0.47, P < 0.01) or radial arteries (mean 1.24,
SD 0.65, P < 0.01). PI values from these vessels were
associated with each other (uterine versus arcuate r = 0.56,
P < 0.01; uterine versus radial r = 0.36, P < 0.01; arcuate
versus radial PI r = 0.40, P < 0.01).

Table I. Characteristics of the study population
<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60</td>
<td>44</td>
<td>35–49</td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>60</td>
<td>5.3</td>
<td>3.0–10.0</td>
</tr>
<tr>
<td>Serum FSH (IU/l)</td>
<td>60</td>
<td>8.1</td>
<td>3.0–37.7</td>
</tr>
</tbody>
</table>

Serum haemoglobin concentrations were assessed by Coulter-
counter T660 (Coulter Electron LTD, London, UK). Serum follicle stimulating hormone (FSH) levels were assessed by an immuno-
fluorometric method (Wallac, Turku, Finland) on peripheral blood
samples taken prior to the TVS examination.
Associations between MBL, PI and other variables were assessed
by Pearson’s product-moment correlation coefficients. Confounding
of the association between MBL and PI by other factors was analysed
using the ordinary least square linear regression. Due to the skewness
of the MBL distribution, the logarithmically transformed values
(logMBL) were used in the analyses. In addition to the uterine artery
PI, independent variables included in the analyses were the size of
the uterus, endometrial thickness, fibroids, menstrual pain, period day,
regularity of cycles, and patient’s age, smoking, parity, contraceptive
method, serum FSH and body mass index (BMI). Age, BMI, serum
FSH, period day, endometrial thickness, and size of the uterus
measured using the average of the uterine width and antero-posterior
diameter were added to the regression models as continuous variables.
The other independent variables were discrete (Table I). The contra-
ceptive method was dichotomized (sterilization, no sterilization).
Besides female sterilization, other contraceptive methods (condom,
male sterilization, no contraception) were not assumed to interfere
with the uterine blood flow.
The study was approved by the Ethics Committee of the Helsinki
University Central Hospital.

FSH = follicle stimulating hormone.
ectasia (dilatations) of the venules in both the myometrium and endometrium of uteri containing leiomyomas, which is associated with menorrhagia (Farrer-Brown et al., 1971). It is possible that there are also other vascular abnormalities resulting from disturbed angiogenesis (Stewart and Novak, 1996). In abnormal vessels, poor contractibility and dysfunction of the haemostatic system may cause menorrhagia (Stewart and Novak, 1996) and decreased impedance.

Estimating uterine blood flow on the basis of PI of colour Doppler ultrasound measurement of uterine artery blood flow has certain limitations. The uterine artery, besides giving vascularity to the uterus, also provides a branch to the ipsilateral ovary, Fallopian tube, and upper vagina. However, the main blood flow is directed to the uterus and therefore the PI best reflects the impedance of the uterine blood flow. Furthermore, the PI does not distinguish between myometrial and endometrial vascular beds. We tried to discriminate this by measuring separately the PI of arcuate and spiral arteries. Although uterine, arcuate and spiral artery PIs were interrelated, no correlation existed between arcuate or spiral PI and MBL. It is not clear whether the signals from endometrial ultrasonography originated from one or more spiral arteriole. Also it is possible to measure arcuate arteries instead of spiral arteries, because the endometrium is thin in the menstrual phase. However, relatively little is known of the perfusion patterns of the endometrium itself.

The physiological events resulting in endometrial shedding at menstruation may be focal. The measurement of the PI of one single spiral artery gives information of only about 1-mm area of the endometrium (Schmidt-Matthiesen, 1963), thus giving limited information of the whole endometrium. The same is true for other modalities used for endometrial blood flow measurements. Laser Doppler fluximetry, a technique assessing red blood cell (RBC) flux in the endometrium via a fibre-optic probe inserted transvaginally into uteri (Gannon et al., 1997, Verco et al., 1998), gives information about endometrial perfusion from a limited area and is also sensitive to cyclic variations. In a thin endometrium it may give information on the myometrial microvascular bed and, in oedematous endometrium, a reduction in endometrial microvascular spatial density would account for a reduction in RBC flux (Gannon et al., 1997). Other measurements of human endometrial perfusion have utilized either clearance of intraluminally or intramurally injected $^{133}$Xe (Fraser et al., 1987), or monitored the clearance of locally applied heat from the endometrium (Akerlund et al., 1975). However, both techniques have their limitations.

In studies of uterine artery PI as measured during period days 1–7 in women with normal menstruation, the mean values of PI have been 3.8 (SD 0.9) (Steer et al., 1990), 2.4 (SD 0.7)
Menorrhagia and uterine artery blood flow


Received on March 23, 1998; accepted on October 7, 1998

References


(Momtaz et al., 1994), and 3.0 (SD 0.6) (Sholtes et al., 1989). In the study of Momtaz et al. (1994), the PI of the uterine artery was 1.4 in women with IUD-induced menorrhagia. In our study the mean PI was 2.20, compatible with figures in the other studies. However, the results of different studies are not fully comparable because of interobserver variability caused by different measuring devices and observer experience.

In our study, 58% of the patients had been sterilized. Verco et al. (1998) found that tubal occlusion increases endometrial perfusion during menstruation as measured by Doppler fluxmetry. However, no subsequent menstrual dysfunction was reported. We found no correlation between the contraceptive method and MBL or PI.

It has been shown by xenon-133 clearance measuring of endometrial blood flow that, in women with ovulatory dysfunctional bleeding, there is not much difference when compared with normal controls but, in women with anovulatory dysfunctional bleeding, the flow rates are exceedingly variable (Fraser et al., 1987). Although 10 (18%) of our patients had irregular menstrual cycles, only five of these patients had a cycle length of more than 32 days, suggesting that very few had anovulatory cycles. Therefore, further subgroup analyses were not meaningful.

Menorrhagia is a significant problem in women of reproductive age, and effective treatment strategies are limited, in part, because of poor understanding of the pathogenesis of the disease. We showed an association between PI of the uterine artery and menstrual blood loss. It is possible that local concentrations of vasoactive compounds simultaneously decrease the blood flow resistance and inhibit normal coagulation. In addition, local dysfunction of vasoactive growth factors or of growth factor receptors in the endometrium may lead to dysregulation of vascular structures and increased uterine blood flow resulting in menorrhagia.

Acknowledgements

The authors gratefully acknowledge Olli Laitinen for the statistical consultation, Ms Seija Puro for the figures and tables and the staff of the Department of Obstetrics and Gynaecology, University of Helsinki.

References


