Endometrial vasculature in Norplant® users: preliminary results from a hysteroscopic study

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Long-acting progestogenic contraceptives are frequently associated with disturbances of menstrual bleeding patterns. In particular, irregular, frequent and prolonged bleeding are commonly seen. The mechanism of this irregular bleeding is unknown, but changes in the endometrial vasculature are thought to be of importance. In endometrial biopsies from Norplant® users, an increase in endometrial microvascular density has been observed after 3-12 months. Morphological changes in endometrial capillaries following progestogen exposure have suggested an increase in vascular fragility. Little is known about the structure and function of the endometrial vasculature in vivo following exposure to exogenous contraceptive steroids. This study has developed techniques for the assessment of vascular fragility by imposing a mechanical stress on the endometrium and observing subsequent bleeding under direct vision. The techniques were used in a preliminary examination between 1 and 9 months after Norplant insertion, and the study identified a number of morphological and functional characteristics of Norplant-exposed endometrium.

Key words: endometrium/hysteroscopy/Norplant/progestogens/vascular

Introduction

Low-dose, long-acting progestogens provide safe, economical and highly effective contraceptive action and are adaptable to a wide variety of delivery systems. They can be reliably used in conditions where oestrogen-containing methods are not appropriate (e.g. during lactation), and are rarely associated with severe unwanted effects. The main disadvantage of progestogen-only preparations is an almost inevitable disruption of menstrual bleeding patterns (Odlind and Fraser, 1990). Acceptance of irregular menstrual bleeding will vary according to the culture, understanding, tolerance and pretreatment counselling of the woman, but bleeding that fails to occur at regular and predictable times is poorly tolerated by many women (Snowden and Christaens, 1983). Irregular bleeding is the single main reason for discontinuation of all progestogen-only contraceptive methods (Belsey et al., 1988).

The Norplant® contraceptive system comprises six silastic capsules which release levonorgestrel at a controlled rate over a 5-6 year period. Norplant is convenient to use and highly effective, but causes disturbances of the menstrual bleeding pattern in 60-100% of women, particularly during the first year of use (McCaulay and Geller, 1992). Episodes of erratic, unpredictable and frequent bleeding are the most troublesome menstrual disturbances, and are the reason for one half or more of all Norplant removals during the first year of use (Odlind and Fraser, 1990).

The mechanism of this change in bleeding pattern remains unclear. Although a wide range of ovarian endocrine and endometrial histology responses are seen in Norplant users, they do not fully explain the large differences in bleeding patterns observed, suggesting that local endometrial vascular and other factors must also play a role.

Normal menstrual bleeding is thought to arise predominantly from spiral arterioles (Markee,
Morphological changes in the endometrial vasculature following prolonged exposure to progestogens suggest that bleeding in these circumstances may be primarily from capillaries and small superficial vessels (Hourihan et al., 1990; Johannisson, 1990). This may account for the characteristic pattern of frequent and prolonged but light bleeding seen in Norplant users (Shoupe et al., 1992).

An increase in superficial endometrial vascular density, with atrophy of the glandular and stromal elements after 3 months of Norplant exposure (Rogers et al., 1993), suggests that the regulation of endometrial growth is disrupted by Norplant. Dilatation of the superficial vessels (Grant, 1969; Maqueo, 1980; Sheppard et al., 1983; Hourihan et al., 1991) and loss of cytokeratin elements in the cytoskeleton (Wonodiresko et al., 1993) suggest that progestogens may alter the integrity of the endometrial vasculature. These changes may increase vascular fragility.

Biopsy may cause substantial disruption of the tissue architecture, and varying conditions when obtaining tissue, such as general or local anaesthesia, may alter endometrial blood flow. When the endometrium is atrophic, hysteroscopic biopsy may not provide sufficient endometrial material for a thorough assessment of vascular characteristics. Furthermore, the morphology of a vessel in vivo may be quite different from that seen in a biopsy specimen.

This study aimed to identify in vivo characteristics of the endometrial vasculature which may contribute to the changes in menstrual bleeding pattern seen following exposure to the progestogen contraceptive implant system Norplant.

Materials and methods

Subjects

A total of 41 women between the ages of 18 and 40 years with regular menstrual cycles who were not using hormonal contraception were recruited through the Family Planning Association, New South Wales (Australia). The volunteers were fully informed about the Norplant system and the study protocol. The likely occurrence of bleeding irregularities was stressed in counselling and in provided written information. All menstrual bleeding or spotting was recorded prospectively on a menstrual bleeding chart.

Endometrial vascular morphology and function were assessed at hysteroscopy in a control group of women with regular menstrual cycles and no history of intermenstrual bleeding. All had an apparently normal endometrium on inspection and on histological analysis.

Informed consent and ethics committee approval (Family Planning Association, New South Wales and The Population Council Institutional Review Board) were obtained for all subjects.

Hysteroscopy

The endometrium was inspected by outpatient hysteroscopy which was performed on two occasions following Norplant insertion. Hysteroscopies were timed so as to observe the development of changes in endometrial vasculature with the duration of progestogen exposure. A Wolf 2.7 mm hysteroscope (Wolf Medical Instruments, Endocorp Pty Ltd, North Ryde, Australia) with a 15 French gauge operating sheath and 7 French gauge rigid biopsy and grasping forceps were used. Saline at room temperature was used for uterine distention at pressures up to 150 mm Hg, and was delivered from 90 cm above the level of the patient. Local anaesthesia into the cervix with 5 ml 1% lignocaine without adrenaline (Astra Pty Ltd, Roseville, Australia) was used in all cases.

Each procedure was recorded on super VHS video, and subsequently reviewed in detail by one of the authors (M.H.). The apparent size, pattern, distribution and density of the superficial and deep endometrial vasculature were noted, including the presence of any unusual vascular features or formations. If bleeding was observed, the size and characteristics of the bleeding vessels were recorded. The characteristics of the glandular and stromal tissue were noted, in particular the apparent extent of endometrial atrophy.

Endometrial observations at hysteroscopy

The following observations were made at hysteroscopy, and reviewed in detail from the video record of the examination.
Glandular and stromal changes
The colour, thickness, texture and regularity of the endometrial stroma were assessed during hysteroscopy and directed biopsy.

Superficial vascular density
Endometrial vascular density was assessed at hysteroscopy by direct inspection of the blood vessels, and graded according to the abundance of superficial vessels observed. Superficial vascular density was reassessed after uterine collapse and redistention.

Vascular morphology
The shape and configuration of superficial and deep endometrial vessels were assessed at hysteroscopy. The presence of regular and irregular (neovascular and mosaic) vascular patterns in superficial and deep vessels was recorded and graded. The presence of petechiae and ecchymoses was recorded. All the above values were regraded after collapse and redistention of the uterus, provided that a clear view of the endometrium could be obtained.

Vascular distribution
The distribution of superficial and deep vasculature in the endometrium was inspected and graded as 'even' or 'patchy'.

Bleeding site
Any report of bleeding before hysteroscopy was recorded. The presence, quantity and source of any bleeding during the procedure were noted and graded. When possible, the origin of any endometrial bleeding was recorded. The size of the bleeding vessel and its relationship to the surface (i.e. coming up through the endometrium at 90° to the surface, or running along the endometrial surface) were noted. Any pattern of the blood loss (oozing, pumping) and the site of the vessel (e.g. as part of a superficial ecchymosis) were noted. When vessels could be emptied, the direction of emptying was noted.

The assessment of vascular fragility
Vascular fragility was assessed by a new technique which imposes a controlled mechanical stress on the endometrial vasculature during hysteroscopy and allows the observation of any subsequent bleeding. When the endometrial cavity had been thoroughly inspected, the saline distention medium inflow was closed and the uterus allowed to empty of fluid by disconnecting the saline from the portal on the operating sheath. As the intrauterine pressure fell, the anterior and posterior uterine walls were observed to collapse, and the quantity and apparent source of any bleeding were recorded. By reconnecting the saline and restoring uterine cavity distention, the endometrium could be reassessed for vascular appearance and bleeding points.

Endometrial biopsies
During the follicular phase of the pretreatment cycle, endometrium was obtained via a Pipelle curette (Pipelle, Cornier, Neuilly, France) and fixed in buffered (10%) formalin solution for 3 h before transfer to phosphate-buffered solution, where it was stored at 4°C before embedding in paraffin wax. Following Norplant insertion, biopsies were taken at each hysteroscopy. A small amount of endometrial tissue was obtained under direct vision using the biopsy forceps (Wolf Medical Instruments) at the end of the hysteroscopy, and further tissue was obtained using a Rocket endometrial biopsy suction curette.

Bleeding patterns
Subjects recorded all episodes of bleeding and spotting on a menstrual bleeding chart. Bleeding patterns were analysed using a 90 day reference period and according to standardized criteria (Belsey et al., 1991) using the menstrual diary analysis system (Suvisaari and Lähteenmäki, 1995). The number of bleeding or spotting days in the 30 days preceding each hysteroscopy was also recorded, and used for a comparison with the hysteroscopic appearance and function of endometrial blood vessels.

Preliminary results
A total of 41 women have been recruited to the study. Of these, seven were excluded during the pretreatment cycle and have not been considered further in the analysis. Only 10 women were identified as suitable controls, and comparisons with this group have yet to be made.

The treatment group was aged between 19 and 40 years (mean 28). The mean cycle length was 28 days. In all, 16 women were nulligravid and
Table I. Timing of hysteroscopy after Norplant® insertion

<table>
<thead>
<tr>
<th>No. of months after insertion of Norplant implants</th>
<th>No. of hysteroscopies performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
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<tr>
<td>5</td>
<td>12</td>
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<tr>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Total number performed</td>
<td>66</td>
</tr>
</tbody>
</table>

Nine out of 34 women (26%) complained that their bleeding patterns were 'problematic' at follow-up. Irregular bleeding and spotting were felt to be the most inconvenient patterns.

Norplant removals

Seven women requested removal of the Norplant implants in the year after insertion (20%; see Table IV). Bleeding or spotting in the 30 day period immediately preceding the hysteroscopy was noted and compared with findings at hysteroscopy. This ranged in duration from 0 to 30 days before the first hysteroscopy (median 9) and from 0 to 26 days before the second hysteroscopy (median 7).

Hysteroscopy

The procedure was well tolerated by the majority of subjects, but two women refused a second procedure because of discomfort on the first occasion. Following amenorrhoea, the procedure was found to be more uncomfortable in a number of subjects.

In all, 24 women (36%) presented for hysteroscopy during a bleeding episode. The apparent shedding of superficial endometrial tissue was observed in almost all of these women. Shedding was rarely observed at other times. In those who presented for hysteroscopy with profuse bleeding and endometrial shedding, it was sometimes difficult to obtain a clear view of the vasculature.

Superficial vascularity at hysteroscopy

The superficial vessels were easily visualized in most cases, but deep vessels were less clearly seen, particularly when the superficial vascular network was extensive. When the endometrium was atrophic, it was often difficult to distinguish deep from superficial vessels. Preliminary results indicate that superficial vascularity appeared to increase following Norplant exposure. This was observed as early as 1 month after Norplant insertion.

The assessment of superficial vascularity was related to the number of days of bleeding or spotting in the previous 30 days. Those with a relatively avascular endometrial surface had experienced less bleeding than those with extensive networks of superficial vessels. Following deflation,

eight were nulliparous. Cervical cytology had been reported as normal in all subjects in the previous 12 months. Endometrial tissue was obtained in the secretory phase of the pretreatment cycle (mean day 22). All Norplant implants were inserted by the authors, or by a supervised practitioner in training. Mild bruising was common after insertion (9/34; 26%), but other complications were rare.

Outpatient hysteroscopy

A total of 66 hysteroscopies have been performed on Norplant users. Two women declined a second hysteroscopy following discomfort during the first procedure. The hysteroscopies were scheduled to provide an impression of the evolving change in endometrial vascular appearance during the initial months following insertion of the implants (Table I).

Bleeding patterns following Norplant insertion

Bleeding patterns were analysed over an average of 309 days (range 169–365). Because Norplant may completely change the normal menstrual pattern, bleeding was assessed over a 90 day reference period (a trimester) and assigned to one or more categories (Table II).

The most frequent patterns of bleeding and spotting observed over the first 6 months of Norplant use were prolonged and irregular bleeding episodes (see Table III). No subjects had only normal bleeding patterns during the follow-up period, while 12 women had amenorrhoea of at least 60 days and six women had amenorrhoea of at least 90 days.

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Table II. Classification of bleeding patterns in women using hormonal contraception (Belsey et al., 1991).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bleeding</td>
<td>No days of bleeding/spotting entered throughout the reference period</td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>Bleeding/spotting episodes lasting &gt;10 consecutive days during a reference period</td>
</tr>
<tr>
<td>Frequent bleeding</td>
<td>More than four bleeding/spotting episodes in one reference period</td>
</tr>
<tr>
<td>Infrequent bleeding</td>
<td>Fewer than two bleeding/spotting episodes in one reference period</td>
</tr>
<tr>
<td>Irregular bleeding</td>
<td>Range of lengths of bleeding/spotting-free intervals exceeding 17 days during the reference period</td>
</tr>
<tr>
<td>Regular bleeding</td>
<td>Two to four bleeding/spotting episodes per reference period, no bleeding/spotting episode lasting &gt;10 days, range of length of bleeding/spotting-free intervals of &lt;17 days</td>
</tr>
</tbody>
</table>

Table III. Bleeding patterns observed in Norplant® users

<table>
<thead>
<tr>
<th></th>
<th>Trimester 1</th>
<th>Trimester 2</th>
<th>Trimester 3</th>
<th>Trimester 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bleeding (%)</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Infrequent B/S (%)</td>
<td>9</td>
<td>18</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Frequent B/S (%)</td>
<td>15</td>
<td>18</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Prolonged B/S (%)</td>
<td>35</td>
<td>44</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>Continuous B/S (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Irregular B/S (%)</td>
<td>68</td>
<td>35</td>
<td>48</td>
<td>27</td>
</tr>
<tr>
<td>Normal B/S (%)</td>
<td>9</td>
<td>9</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>No. of trimesters analysed</td>
<td>34</td>
<td>34</td>
<td>27</td>
<td>22</td>
</tr>
</tbody>
</table>

B/S = bleeding or spotting.

Table IV. Reasons for Norplant® removal

<table>
<thead>
<tr>
<th>Reason for Norplant removal</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive bleeding/spotting</td>
<td>5</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>1</td>
</tr>
<tr>
<td>Subject wished return of fertility</td>
<td>1</td>
</tr>
</tbody>
</table>

and redistention of the uterus, the apparent superficial vascularity was increased.

Vascular patterns

In almost all cases, the superficial vascular distribution was 'patchy' (i.e. areas of dense vascularity adjacent to areas that appeared pale and relatively avascular). This was evident from 1 month of Norplant exposure, and persisted over time.

Superficial vascular patterns were rarely regular. Neovascular patterns with a single vessel stem and fine branches, mosaic or reticular patterns were commonly observed (Figure 1).

Dilated superficial vessels were observed in approximately one-third of cases. Preliminary results suggest that those with dilated vessels observed at hysteroscopy had experienced more breakthrough bleeding in the previous 30 days.

Petechiae and ecchymoses

An unexpected finding was the predominance of petechiae and ecchymoses in the endometrium of Norplant users. They were observed as early as 1 month after insertion of the implants (Figure 2). In some cases, these areas of subepithelial bleeding were observed to form immediately after deflation and redistention of the cavity.

Vascular fragility

Bleeding at deflation and reflation of the uterine cavity was observed in almost all women in the treatment group, and was profuse in approximately half the subjects tested. Profuse bleeding was commonly observed in those who had experienced breakthrough bleeding in the previous month, and in those who presented for hysteroscopy during a bleeding episode. Preliminary observations in the control population indicate that bleeding is not a normal occurrence when this mechanical stress is imposed on the endometrial vasculature.
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Figure 1. Hysteroscopic appearance of superficial endometrial vessels showing neovascularization 4 months after the insertion of Norplant®. Endoscopic biopsy forceps illustrate the size of the vessels (forceps diameter 2 mm).

Figure 2. Hysteroscopic appearance of superficial endometrial vessels showing ecchymoses 6 months after the insertion of Norplant®. Endoscopic biopsy forceps illustrate the size of the vessels (forceps diameter 2 mm).

**Bleeding site**

Where the size of the bleeding vessel could be assessed, those who presented for hysteroscopy during a bleed appeared to be bleeding from large veins. In a further 20 cases (30%), bleeding was observed to start during the hysteroscopy. Bleeding appeared to arise from small capillaries and venules in these circumstances. Bleeding from petechiae and ecchymoses was commonly observed, particularly when bleeding appeared to start during the procedure. By reducing the intrauterine pressure during hysteroscopy, bleeding could often be provoked.

**Discussion**

The observation of endometrial vessels *in vivo* provides new and significant information about the effects of long-term low-dose progestogens on the endometrium.

Outpatient hysteroscopy appeared to be acceptable to the majority of women tested. In this
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study, the operating sheath made the hysteroscope diameter 5 mm. For some nulligravid women, this may be too large to permit easy access to the uterine cavity. Subjects were assessed before inclusion in the trial by the insertion of a sterile uterine sound without analgesia. Significant discomfort during this examination excluded two nulligravid women from inclusion in the trial.

The use of an endoscopic camera allowed the hysteroscopic examination to be displayed on a monitor. This provided a clear image for the surgeon, and interesting viewing for the patient. In this study, the subjects were fully aware of our interest in the endometrial vasculature, and were often fascinated by the appearance of their endometrium on screen. A video recorder was essential for later examination of the hysteroscopic findings. Using a super VHS recorder produced high quality images and improved picture clarity. The video laser printer was not essential, but allowed selected still photographs to be used with the image analyser for the purpose of vascular measurement, and obviated the need for repeat video searches.

Endometrial vasculature is sensitive to changes in the ambient environment. In this study, saline was used for uterine distention because it allowed a clearer view of the endometrium during a bleeding episode than carbon dioxide. It is possible that a viscous liquid distention medium (such as dextran) could improve clarity further. The temperature and pressure of the distention medium may also influence the endometrial vasculature. Further studies with body temperature (37°C) saline and graduated intrauterine pressures are ongoing. Similarly, agents used for local analgesia, particularly those containing adrenaline, are likely to influence uterine blood flow and endometrial vascularity. Non-steroidal anti-inflammatory preparations taken before the hysteroscopy may also influence endometrial vascular appearance, and in particular vascular fragility. In this study, all subjects (including controls) were advised to take mefanamic acid 1 h before the procedure.

Because there is little information available about the endometrial vasculature in the normal subject at hysteroscopy, an assessment of each Norplant user in the pretreatment cycle would have provided valuable information but could not be included in the original study protocol for ethical reasons. The control group consisted of women with regular cycles who were not taking hormonal preparations and had a normal macroscopic and microscopic appearance of the endometrium. However, each of these women had a gynaecological complaint (usually menorrhagia) such that the function of the endometrial vasculature may not be entirely normal.

The bleeding patterns observed in this population displayed the characteristic changes of increased frequency and length of bleeding episodes, with irregular bleeding and spotting commonly observed following Norplant exposure (Shoupe et al., 1992). Cultural variations are known to profoundly influence menstrual bleeding patterns in users of hormonal contraception (Belsey et al., 1991). It is unclear whether the source of this variation is related to weight, diet or other factors.

Tolerance of irregular bleeding was high in this study. The majority of subjects had used a wide variety of other contraceptive methods and had come to Norplant as a 'last resort'. Commitment to a clinical trial may also have increased tolerance of menstrual disruption. Those who requested removal had experienced (on average) only 17 days free of bleeding/spotting in the previous 90 days.

Immunohistochemical analyses of biopsies from Norplant users have shown that endometrial vascular density is increased significantly at 3–12 months of use (Rogers et al., 1993), while exposure to high-dose progestogens appears to decrease vascular density (Song et al., 1995). In this study, endometrial vascularity was apparently increased in Norplant users as early as 1 month after insertion of the implants, and the degree of vascularity was related to recent breakthrough bleeding.

It is unclear whether the increased vascular density observed by Rogers et al. (1993) is due to a genuine vascular proliferation or is related to atrophy of the endometrial glandular and stromal elements. Endometrial endothelial cells do not appear to be actively proliferating at 3–12 months after the insertion of Norplant (Gooder and Rogers, 1994), but it is possible that the proliferative period occurred earlier than 3 months. It is also possible that angiogenesis in the endometrium...
may occur by mechanisms not detected by the technique of endothelial cell proliferation used in this study. The predominance of irregular and neovascular patterns suggests that erratic angiogenesis may be occurring. A 'blind' endometrial biopsy may miss these abnormal vascular formations.

Stromal vascular distribution in the normal endometrium is thought to be uniform throughout the uterine cavity (Shaw et al., 1979; Dallenbach-Hellweg, 1987). This was rarely observed in Norplant users. Rogers et al. (1993) found no apparent histological or vascular differences in endometrial tissue from 'bleeding' and 'non-bleeding' sites in Norplant users. However, blind biopsies may not reliably indicate vascular changes when vascular distribution is so patchy. Unfortunately, the available endoscopic direct vision biopsy instruments do not provide biopsies of adequate size for meaningful analysis.

The presence of dilated endometrial blood vessels in users of long-acting progestogens has been debated from histological (Grant, 1969; Maqueo, 1980; Ludwig, 1982; Hourihan et al., 1991) and hysteroscopic (Fraser and Peek, 1992) observations. This is the first time that these vessels have been systematically inspected in vivo. The dilated vessels appeared to be veins, and could often be emptied by pressure from the biopsy forceps. Dilatation may represent a loss of structural integrity in superficial vessels, changes in pressure or flow in the endometrial vasculature, or the active growth of abnormal, enlarged thin-walled vessels. Studies are in progress to assess endometrial blood flow in Norplant users before and after insertion of the implants. Dilated vessels may also indicate endometrial atrophy, displaying deep vessels on the endometrial surface. An apparent association was observed between dilated vessels and breakthrough bleeding.

The predominance of petechiae and ecchymoses in Norplant-exposed endometrium was an unexpected finding. These purpura are discoulourations of the epithelium caused by subepithelial haemorrhage, and must arise from disturbances in vascular integrity, perhaps exacerbated by local disturbances of clotting mechanisms. Purpura commonly indicate capillary fragility, and are found in the dermal epithelium in the elderly or in patients exposed to corticosteroids (Rook et al., 1986). Minor trauma may exacerbate purpura. When a vessel has ruptured beneath the epithelium, it is the epithelial integrity which dictates whether subepithelial purpura or frank bleeding are observed. Purpura are rarely seen in the endometrium in normal subjects. In spontaneous atrophy, purpura may occur in an avascular endometrium, and are provoked by distention of the uterus (Hamou, 1981). In the Norplant-exposed endometrium, purpura were often evident immediately on entering the uterus, and were also observed developing following pressure from the forceps and emptying of the cavity. This may indicate fragility of the superficial endometrial vasculature.

Where ecchymoses contained punctated gland openings, the hysteroscopic picture was very similar to the appearance of classic endometritis. White cells are thought to be involved in the initiation of normal menstrual bleeding (Bulmer et al., 1987; Kamat and Issacson, 1987) and are located near blood vessels in the endometrium, where they may influence vascular permeability and integrity. Leukocytes may release a number of substances into endometrial tissue which can cause cellular and tissue breakdown. Polymorphs also appear in the focal endometrial necrosis associated with high-dose progestogens (Fraser and Peek, 1992; Song et al., 1995).

The development of this test of vascular fragility was based on observations that women using high-dose progestogens could easily be induced to bleed during hysteroscopy by deflation and reflation of the uterine cavity (Fraser and Peek, 1992). In this study, profuse bleeding on collapse and redistention of the uterine cavity was commonly observed in Norplant users and was associated with an increase in breakthrough bleeding. Increased bleeding may be caused by widespread vascular fragility with more vessels bleeding, or by bleeding from larger vessels. Hysteroscopic observations suggest that bleeding from larger vessels mainly accounts for profuse bleeding on collapse of the uterus.

The site of bleeding in progestogen-induced breakthrough bleeding was previously unknown. Biopsy specimens have rarely been able to identify the precise breach in the endothelium and epithelium that produced clinically evident bleeding.
There is little systematic evidence from in-vivo studies to support the suggestion that normal menstrual bleeding arises from the spiral arterioles, and breakthrough bleeding from small vessels and capillaries. Bleeding from a wide variety of vessels was observed in this study. In general, the larger bleeding vessels seemed to be large venules: they could be emptied with pressure and run parallel to the surface of the endometrium. Occasionally, vessels that appeared to be arterioles, running perpendicular to the endometrial surface and showing 'pumping' blood loss, were observed. Based on Markee's (1940) observations, normal menstrual loss is thought to arise predominantly when spiral arterioles empty blood enclosed during tight coiling in the secretory phase of the menstrual cycle. Emptying of these vessels would not be expected to 'pump' into the cavity. Commonly, very small vessels and areas of petechiae and ecchymoses were seen to bleed. This bleeding often appeared to start during the hysteroscopic examination, particularly after redistention of the cavity.

The role of mechanical stress in the initiation of bleeding may be important in spontaneous menstrual bleeding, particularly when vessels are made vulnerable by lack of stromal support because of endometrial atrophy. Several Norplant users commented that exercise seemed to provoke episodes of spotting, and almost all women bled or spotted for several days after the hysteroscopy. Fragile or exposed superficial blood vessels may experience mechanical stress in vivo from small shearing actions of the opposing endometrial surface. The normal uterus is mobile in the pelvis and is likely to move with physical exertion, such that exercise may provoke bleeding.

In summary, a detailed hysteroscopic inspection of the endometrium in Norplant users demonstrates functional and morphological changes in the endometrial vasculature which may help to explain the characteristic alterations in bleeding patterns observed in users of long-term progestogen-only contraception.

Acknowledgements

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