A re-appraisal of the morphological changes within the endometrium during menstruation: a hysteroscopic, histological and scanning electron microscopic study

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BACKGROUND: The morphological changes occurring during the dynamic process of menstruation have previously been described only in terms of data derived from static sources, including histological and electron microscopic studies. Recent advances in pressure-controlled, continuous flow hysteroscopy permit dynamic images to complement the traditional modalities.

METHODS: A prospective observational study of 15 women (age range 22–52 years) during various phases of active menstrual shedding and repair using the novel hysteroscopic plus histological and scanning electron microscopic approaches. The women had not taken hormonal therapy in the previous 2 months and all had regular menstrual cycles of 27–30 days.

RESULTS: For the first time, the hysteroscopic appearance of the endometrium during menstruation has been documented. This technique indicates that endometrial loss and regeneration are piecemeal processes that occur simultaneously in different areas of the uterine cavity. The exposed basalis endometrium is rapidly covered with a fibrinous mesh, upon and within which new surface epithelial cells develop. New epithelial cells appeared to arise from the underlying stromal cells rather than as epithelial outgrowths from the residual gland stumps as had previously been thought.

CONCLUSIONS: Endometrial surface epithelial regeneration is a rapid, localized and piecemeal process that appears to occur as a consequence of cellular differentiation from stromal cells within the residual basalis.

Key words: menstruation / epithelial regeneration / hysteroscopy / scanning electron microscopy / histology

Introduction

The menstrual shedding and subsequent repair of the surface endometrium is a process unique to humans and the higher primates. A knowledge of the mechanisms controlling this fundamental biological process is essential to our understanding of factors affecting both reproduction and many gynaecological disorders that reduce the quality of life of women.

The endometrium is a dynamic tissue that, in response to the cyclical changes in levels of estrogen and progesterone, undergoes recurrent proliferation, differentiation and tissue breakdown (Salamonsen, 2003; Jabbour et al., 2006). The tissue remodelling associated with menstrual shedding and repair occurs rapidly, but most observations of this process have been conducted using static histological and other laboratory investigations.

The histological changes within the endometrium during menstruation were described by Novak and Te Linde (1924). They concluded that new surface endometrial epithelium arises chiefly as outgrowths from the basal stumps of the uterine glands. This conclusion was supported by others (Herrel and Broders, 1935; Sturgis and Meigs, 1936; McLennan and Rydell, 1965). More dynamic support for this theory was developed by Markee (1940). Using an endometrial transplant into the rhesus monkey eye model, he emphasized the importance of vascular changes in the process and also demonstrated the speed of epithelial repair. This mechanism of epithelial regeneration from basal glands was further supported by the scanning electron microscopic studies of Ferenczy (1976), Ludwig and Metzger (1976) and Ludwig et al. (1988), and this theory is currently the accepted dogma of how the endometrial epithelium regenerates (Salamonsen, 2003). The theory is underpinned by the concept that mature adult...
cells can only arise from cells of a similar adult differentiated type (i.e. epithelial cells can only arise from similar epithelial cells). Recent work raises the possibility of an alternative mechanism of endometrial repair based on differentiation from endometrial (Gargett et al., 2007; Lynch et al., 2007) and/or circulating progenitor cells (Bratincsak et al., 2007).

Hysteroscopic inspection of the internal surfaces of the uterine cavity for diagnostic and therapeutic purposes is now a routine gynaecological procedure. This technique allows the detailed and dynamic inspection over time of the anatomy and pathology of the endometrial surface. The procedure requires the distension of the uterine cavity with fluid under pressure. The development of continuous flow hysteroscopy and increased understanding of the effects of controlling and altering the intrauterine pressure (IUP) of the distension fluid (Hasham et al., 1992) permits the direct in vivo visualization of the endometrium throughout the menstrual cycle. The hysteroscopic appearances of the surface endometrium during menstruation have not yet been formally documented.

The ability to perform hysteroscopy at all stages of the menstrual cycle combined with the new concepts about the mechanisms of endometrial repair prompted this study in the hope of increasing our understanding of the dynamics of menstrual shedding and regeneration.

Materials and Methods

This is a prospective descriptive study of 15 patients undergoing pressure-controlled hysteroscopy during the active bleeding phase of the menstrual cycle. Each gave informed consent for the procedure that was performed as part of their routine gynaecological assessment. The protocol was approved by the King Edward Memorial Ethics committee.

All hysteroscopies were performed on women of menstrual age (range 22–52 years), none of whom had taken hormonal therapy in the 2 months prior to surgery. They all had regular menstrual cycles of between 27 and 30 days and bleeding lasting between 4 and 8 days. The appearances of the endometrium during the days of active bleeding were so variable that histological dating was not possible. Cycle dating was therefore based only on the women’s description of the time of onset of menstrual bleeding. This was collected prospectively in terms of hours since first observation of established blood loss. Of the 15 patients, 5 stated that they had begun to menstruate on the day of the examination (Day 1), 5 were in the second day, 3 on the third day, 1 on the fourth day of bleeding and 1 on the fifth day. In addition, one patient was in the 28th day of regular 28-day cycles, and this group alone had dating confirmed histologically according to the criteria of Noyes et al. (1950).

The hysteroscopy was performed immediately prior to hysterectomy in 4 patients and prior to curettage in the remaining 11 cases. Full thickness endometrial specimens were available for histological and scanning electron microscope (SEM) study in the hysteroscopy group. In the remaining 11 cases, endometrium was obtained by deep, sharp curettage with an attempt to obtain basal endometrium and the endo-myometrial junction in the specimen. Deep endometrium and myometrium was successfully obtained in 9 of the 11 cases. Specimens were only subjected to detailed analysis when either surface epithelium or subepithelial myometrium was included in the specimen to facilitate orientation. Diagnostic curettage or hysterectomy was performed for the following indications: menorrhagia/dysfunctional uterine bleeding in eight cases, endometriosis in three, fibroids in three, extensive adenomyosis in one, inter menstrual bleeding in one, infertility and assessment prior to oocyte donation in one and pelvic pain in one. The total adds to more than 15 as four patients had two pathologies present.

Hysteroscopy

Using a standard 5 mm diagnostic hysteroscope (Storz, Tuttingingham, Germany), the uterine cavity was distended using 0.9% normal saline under pressure either using a pressure-controlled rotary pump (Storz) or gravity feed from a flexible infusion bottle surrounded by a blood-pressure type of cuff. Using a method we have previously described (Hasham et al., 1992), crystal clear views of the uterine cavity may be obtained at all stages of the menstrual cycle even during phases of active menstrual bleeding. Blood loss can be controlled by elevating the IUP of the distension medium above the mean arterial pressure (100 mg/Hg). At this pressure, all bleeding points are effectively tamponaded and bleeding ceases. Using a continuous flow hysteroscope, pressurized circulation of distension fluid can flush out retained blood and clots, producing a clear cavity that enables details of the endometrial surface to be inspected. Careful controlled reduction of the IUP by either reducing the infusion pressure and/or partially opening the outflow channel allows bleeding to re-establish and individual bleeding points to be defined. This cycle of raising and lowering the IUP can be repeated and reversed at will.

Scanning electron microscopy

Squares of endometrium measuring about 10 mm² were obtained following dilatation and curettage or hysterectomy surgery. The tissues were pinned out using 26G needles with the surface epithelium uppermost and immersed in 2.5% of glutaraldehyde in 0.01 M phosphate-buffered saline, pH 7.4, for 18 h at 4°C. The tissues were then dehydrated and critical point dried. The dried samples were coated with both carbon and gold and viewed using a Zeiss 1555 Supra variable pressure FESEM or a Philips 505 SEM. Images were captured digitally as TIFF files.

Histology

Endometrial biopsies were fixed in 10% of formalin for 18 h and were embedded in paraffin. All underwent a standard haematoxylin and eosin (H&E) stain and were given to an experienced histopathologist for histological dating according to the criteria of Noyes et al. (1950) when applicable and identification of any pathological features.

Results

The mean age of the patients was 37 years (range 22–52 years). The number of study patients in each phase of the cycle is shown in Table I. The hysteroscopic appearances of the surface epithelium were quantified according to the presence or absence of characteristic surface epithelium indicating unshed endometrium, the presence or absence of tubular structures indicating recently shed surface endometrium and the presence or absence of characteristic new surface epithelium and underlying vascular network suggesting regenerated surface epithelium. This semi-quantitative method allows a visual summation of the relative distribution of the three main hysteroscopic appearances during the cycle. Each + represents 20% of the surface expressing a particular feature. Table I indicates the piecemeal nature of the shedding, but that classic late secretory phase appearance is progressively replaced first by ragged, multi-tubular appearance (fronds) and subsequently by tense new surface epithelium with an extensive but often incompletely remodelled vascular network.
Phase 1: the immediate premenstrual appearance

Intrauterine fluid under fairly high pressure (>80 mm/Hg) is instilled to compress the surface epithelium. This results in many of the minor surface irregularities being flattened with obscuration of much of the superficial thin-walled vascular system. Lowering the pressure of the distension fluid allows the compressed endometrium to expand and appear to be thicker, softer and more distensible. It will also permit detailed inspection of the now decompressed superficial vascular system. We cannot rule out that the repeated and rapid changes in IUP do, in themselves, induce morphological changes within the endometrium. We have, however, repeated these observations (unpublished data) and believed that the appearances are consistent and unlikely to be induced by the pressure and flow changes described.

At lower IUP, the hysteroscopic appearance of the surface epithelium endometrium on Day 28 is of a flat semi-translucent pinkish tissue (Fig. 1A). Under these conditions, an extensive blood vessel system may be observed running beneath and parallel to this luminal epithelium. This subepithelial, horizontally distributed blood vessel system can also be demonstrated on standard H&E histological preparations (Fig. 1B).

The endometrium in the immediate premenstrual phase is fragile and lacking elasticity. During hysteroscopy, deep permanent furrows can readily be produced by lightly dragging a hysteroscopic instrument across its surface (Fig. 1C). The semi-translucent nature of the endometrial structure allows individual glands to be defined with the hysteroscope. The glands in the late secretory phase are lined with tall columnar epithelial cells that are covered on their external surfaces with microvilli. The scanning electron microscopic appearance of the immediate premenstrual epithelium clearly demonstrates the tall columnar nature of the cells with their multiple microvilli interspersed with ciliated cells of an identical appearance to cells lining the glands at this stage (Fig. 1D). The make-up of the endometrium in the immediate premenstrual phase is well demonstrated in the unusual sagittal section SEM (Fig. 1E). This demonstrates the crowded, much coiled secretory glands and their close relationship with the ascending spiral arterioles. The seldom recognized transverse running branches of these vessels are also well demonstrated in this section.

Phase 2: early zonal endometrial shedding

The first hysteroscopic sign of menstruation is the appearance of extensive subepithelial haemorrhage and the development of linear cracks (Fig. 2A). This is followed by separation of pieces of superficial endometrium from the underlying deep stroma. This is at first partial (Fig. 2B) and gradually extends until a complete zone becomes detached (Fig. 2C). These pieces are of variable size but usually of substantial thickness and consist of pinky-red surface epithelium and grey superficial underlying glands and stroma. These pieces become progressively undermined along a cleavage plane and may move vigorously in the distension fluid current until they become completely detached and float free within the cavity. The most striking feature of this shedding is its piecemeal nature. Areas of shedding are at first localized and surrounded by extensive areas of unshed endometrium (Fig. 2D), and the shed areas progressively coalesce leaving reducing islands of unshed superficial endometrium (Fig. 2E and F).

This process of progressive shedding is spread over several days and before it is completed there are areas of obvious surface repair and healing. At any time during the phase of active bleeding, areas of unshed, partially shed, completely shed and healing endometrium can be seen to coexist. Shedding and repair of the endometrium is a local and not a generalized process. This zonal nature of tissue shedding and repair may have important physiological and clinical consequences.

<table>
<thead>
<tr>
<th>Day of patient</th>
<th>Cycle</th>
<th>Proportion of unshed endometrium</th>
<th>Proportion with endometrial fronds</th>
<th>Proportion with healed endometrium</th>
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<tbody>
<tr>
<td>Day 28</td>
<td>1</td>
<td>++++</td>
<td>-</td>
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<tr>
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<td>2</td>
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<td>Day 28</td>
<td>4</td>
<td>+++</td>
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<td>Day 28</td>
<td>5</td>
<td>+++</td>
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<td>Day 28</td>
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<td>Day 28</td>
<td>8</td>
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<td>+</td>
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<td>Day 28</td>
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<td>+</td>
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<td>-</td>
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<td>Day 5</td>
<td>15</td>
<td>+</td>
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Each + represents 20% of the surface expressing a particular feature.
Phase 3: later zonal shedding

Both the lower surfaces of the separated superficial and the upper surfaces of the retained basalis endometrium are quite irregular. Stromal cells and supporting framework appear to readily disperse into the menstrual loss, leaving the torn ends of both glands and blood vessels as prominent semi-translucent tubes protruding from the residual basal endometrium which can be readily seen during hysteroscopy (Fig. 3A) and conventional histology (Fig. 3B). Many of the semi-transparent tubes are the basal portions of the torn glands, and their characteristic structure of a single layer of columnar epithelium lined with microvilli can readily be appreciated on the SEM image (Fig. 3C). Some of the “tubes” are, however, blood vessels that may be still patent and can be observed to bleed actively from their distal ends when the IUP is reduced (Fig. 3D).

The dramatic appearance of multiple endometrial glands and vessels waving in the current of the distension medium is a brief, temporary phase in the process of the piecemeal shedding. The fate of the tubular structures is not certain, some may further detach in a second phase of shedding, leaving very short residual stumps that protrude just above the residual endometrial stroma. When not disturbed by the distension fluids they lie parallel with the healing surface, and it is possible that some of the glands and perhaps many of the thin-walled blood vessels may be incorporated within the rapid repair that occurs within the basalis at this time. Whatever their fate, they become much less prominent on hysteroscopic examination within 1 – 2 days of endometrial shedding. In each area, the exposed glands and vessels are friable and their phase of prominence is transitory. When the exposed tubes are no longer visible, the exposed surface of the residual basalis takes on a relatively flat grayish/white appearance that is rather ‘granular’ (Fig. 3E). Once the superficial endometrium is shed, the exposed surface becomes covered with a fibrinous matrix (Fig. 3F).

Phase 4: healing of the surface epithelium

The characteristic hysteroscopic appearance of the surface repair of endometrium in the healing phase is the presence of a smooth, tense, white surface layer with few irregularities or asperities.

New epithelial cells appear scattered across the fibrinous matrix (Fig. 4A). In the earliest stages of healing, they may be seen as single cells or are found in small groups, sometimes around the residual glandular stumps, sometimes near exposed blood vessels, but in the earliest phases of healing they are often found, contrary to earlier concepts, isolated and in no direct communication with mature cells at the torn distal end of the basal glands (Fig. 4B).

Repair of the endometrium, as with its shedding, is a piecemeal process with areas of new surface epithelium interspersed between granular areas of uncovered endometrium (Fig. 4C).
The new surface epithelial cells are predominantly low cuboidal cells with central nuclei prominently seen within the otherwise rather flattened cells. The surfaces of these new luminal epithelial cells are predominantly smooth and, unlike the surfaces of cells of the premenstrual endometrium, contain few or no microvilli and ciliated cells are rare (Fig. 4D). The appearance of these new cells contrasts sharply with that of the cells lining the glandular stumps.

The remodelled superficial vascular system can be seen through the newly formed surface epithelial layer. Progressively reducing the IUP allows the still damaged areas of the vessels to be defined (Fig. 4E). The final stage of healing is when the integrity of both the surface epithelium and the underlying vasculature is completed (Fig. 4F).

**Discussion**

It is widely accepted that endometrial loss at the end of the menstrual cycle occurs as a consequence of the rapid reduction in the levels of progesterone and estrogen. These changes in steroid levels provoke
interaction with different cognate nuclear receptors, resulting in a complex cascade of local factors within the endometrium which act in an autocrine/paracrine manner (Jabbour, 2006). The mechanisms controlling this process are complex and still poorly understood. This paper investigated some of the structural and anatomical changes associated with this process using a number of investigative modalities.

Ferenczy (1976) using scanning electron microscopy noted that the degree of endometrial destruction displayed no topical uniformity in uteri studied at the same cycle day. Our hysteroscopic and SEM examinations take this observation further and emphasize that the shedding process occurs in zones. The whole endometrial surface or even a single sample of endometrium can contain endometrium in a variety of forms. Unshed, shedding, completely shed and repaired...
endometrium can coexist. Previously undocumented panoramic hysteroscopic views of the whole of the endometrium display this phenomenon clearly. With this technology, the true patchy, zonal nature of the endometrial loss is apparent. In the horizontal plane, an area of endometrium may become detached hours or days before its immediately adjacent areas. In the vertical plane, the most luminal areas of the endometrium initially become detached, thereby exposing glands and vessels that protrude above the cellular stroma of the basalis. Subsequently, these exposed tubes become less obvious, and the surface becomes remodelled and covered by

Figure 4 Healing surface of endometrium. (A) A SEM image of a Day 2 endometrium whose surface is covered with a fibrin matrix. There are numerous, apparently new, epithelial cells arising across this surface. These do not appear to be related to glands but in the top right-hand corner of the image (arrow), a group of cells appear to be intimately related to a blood vessel. (B) A SEM image of a Day 2 specimen that shows the fibrin matrix partially surrounding an exposed gland stump. New cells are developing on both the matrix and the exterior surface of the gland. Note the microvilli on the cells making up the everted edge of an endometrial gland and the very different physical appearance of the ‘new’ surface epithelial cells without microvilli that are lying within the microvilli, within and on the fibrinous matrix. (C) The hysteroscopic appearance of the surface on Day 3 of the cycle. Most of the surface appears to be covered with new epithelial cells, but the area defined by the two black arrows remains unrepaired with new surface epithelium. (D) A SEM image of almost completely regenerated surface epithelium. The cells of the new surface epithelium are irregular in shape and size but are essentially small and cuboidal in shape contrasting with the tall columnar epithelium of late secretory phase endometrium and the epithelium lining residual gland stumps illustrated in previous images. (E) A hysteroscopic view of an area at Day 3 of menstruation during low-pressure examination. The epithelium appears thin and white with extensive horizontally running vascular subepithelial plexus from which active bleeding persists from a single pin-point opening (arrow). (F) A stained histological specimen (H&E) of a Day 3 endometrium. Here, the surface has been re-covered with cuboidal epithelial cells and these merge with the columnar epithelial cells within the residual gland.
cellular stroma to produce a fairly flat surface layer of residual basalis that then rapidly recovers with a layer of thin epithelial cells. Phased shedding occurred adjacent to, and simultaneous with, the early stages of endometrial repair. We concluded that unlike other stages of the menstrual cycle where accurate dating using precise histological criteria is possible, there is no ‘typical’ picture for any day during the menstrual phase of the cycle. Any observation or calculation taken during the menstrual phase must take into account the zonal level of the sample and the proportion of the specimen containing late secretory unshed, currently shedding, totally shed and healing endometrium. Without such data, measurements of endometrial function that are taken in the menstrual phase may be of very limited value. Importantly, zonal loss and repair suggests the concept that the mechanisms controlling endometrial loss are focal and related to local factors, while under the general influence of systemic hormonal changes.

The rapidity with which the integrity of surface epithelium of the endometrium is restored after its programmed shedding is remarkable. Equally remarkable is the speed with which the integrity of the circulation is restored. Surface repair without concomitant vascular repair would merely result in the collection of much subepithelial blood as haematomata. All the terminal branches of the vertically ascending spiral endometrial arterioles are torn, and all the extensive subepithelial and many of the intra-endometrial transverse vascular networks are lost. This results in an extensive exposed endometrial surface with vast numbers of individual bleeding points. Bleeding occurs from both the tips of damaged vessels and from small holes in the re-forming vascular systems. Our observations suggest that significant lengths of ‘skeletonized’ endometrial vessels may be retained when the surrounding epithelium and stroma is shed. Such unshed vessels may then remodel and incorporate into the new vascular system which is usually completely reconstituted within 2–4 days of shedding. These findings extend the observations of Christiaens et al. (1980). Individual areas of vascular repair, however, occur more rapidly and an area may have a complex vascular system restored within hours or even minutes of disruption.

The reasons for the cyclical programmed loss of the superficial layers of the endometrium in humans and the higher primates are outside the scope of this paper. The consequences of the process are that menstruating women have recurrent extensive open wounds and massive disruption of the vascular system on a scale without parallel in the physiological world. These events can threaten both overwhelming infection and catastrophic haemorrhage. Urgent repair of this intentional damage is clearly essential. We suggest that this is facilitated in a number of ways that have not previously been defined.

The process of endometrial loss is a piecemeal one. Our work confirms that of Nogales-Ortiz et al. (1978). Some areas have not begun to shed while other areas are actively shedding while still others are in the process of repair and others are already completely resurfaced. This staged shedding ensures that the extent of exposed endometrium and the number of damaged vessels at any particular moment is as low as possible. Staged shedding and rapid repair of each shed zone mini-mizes the area of exposed and bleeding surfaces, thereby minimizing the risks of infection and haemorrhage. This process is probably associated with significant biological advantages, but it poses real problems for medical researchers who, traditionally, wish to classify menstrual endometrium as Day 1, Day 2, etc. In fact each menstrual day may contain areas of unshed, late secretory phase endometrium together with partially or completely shed and partially or completely healed endometrium. Any attempt to homogenize or average out measurements of the structure during menstruation may result in misleading results. The 15 women in this study presented with a variety of pathologies, which could have influenced the way in which menstrual breakdown occurred. It is not known how various uterine and endo-metrial pathologies affect the processes of menstrual shedding. Endo-metriosis is often associated with premenstrual spotting, whereas fibroids, adenomyosis and polyps may be associated with heavy and/or prolonged bleeding. It is possible that the results of this small series may be distorted by the presence of these pathologies. It is not ethical to obtain tissue from healthy women and as the patterns observed seem to be consistent, whatever the pathology, we believe they represent the mechanisms associated with this basic physiological process.

The most widely accepted theory of luminal epithelial repair is that the surface epithelium develops primarily from proliferation of epithelial cells from the tips of the gland stumps (Ferencycz, 1976; Ludwig et al., 1988; Salamonsen et al., 2002). Our observations do not support this hypothesis. We note that the healing endometrial surface first becomes covered with a fibrinous matrix within which blood and other cells become trapped. It is on this matrix that the new surface epithelium develops. In the early stages of repair, single isolated or small islands of new epithelial cells are observed. These islands ultimately coalesce and fuse to produce a new surface epithelium. These new cuboidal cells are frequently not in direct contact with the glandular columnar cells and do not appear to arise from them. These new epithelial cells eventually fuse with, but do not obviously arise from, the mature cells lining the glands.

In addition to this previously unreported distribution of new surface epithelial cells away from glandular stump, the morphology of the new epithelial cells is significantly different from that of late secretory phase. New cells have a predominantly smooth surface and are low cuboidal in shape and strikingly without microvilli. In contrast, late secretory phase cells are large columnar cells with marked microvilli associated with multiple interspersed ciliated cells. During remodelling of the surface epithelium after menstruation, these new cuboidal cells are not inevitably in direct contact with the columnar cells and do not appear to arise from them. The mature tall glandular columnar cells covered with microvilli eventually fuse with the new, low cuboidal cells lacking microvilli but do not usually start in continuity. It is unlikely that mature well-differentiated ciliated and microvilli columnar epithelial cells could give rise to more immature smooth-surfaced cuboidal cells.

These observations suggest that the new endometrial surface epithelium does not arise, as currently accepted, as a result of direct extension from the residual basal epithelial glands but rather as a result of differentiation of cells from within the endometrial stroma. This theory has long been considered (Baggish, 1967) but has not gained wide acceptance. Our observations into the distribution and morphology of the new epithelium are compatible with this alternative hypothesis. We are currently conducting further studies to investigate the nature of these fundamental processes of endometrial shedding and repair.
Conclusions

Hysteroscopy, SEM and conventional histology provide complementary information about the changes in the surface appearance of the endometrium throughout the menstrual cycle. Correlation of these dynamic and static imaging systems allows new insights into the mechanisms involved in menstruation.

Using these modalities, we observed that menstrual shedding occurs in a piecemeal manner. Areas of unshed, shedding and healing endometrium coexist. This can confuse many objective clinical and research assessments of menstruation but may have physiological advantages.

Our observations suggest that new surface epithelial cells may develop from underlying stromal cells rather than by division and expansion of epithelial cells from the tips of the glandular remnants.

Shedding and replacement of the endometrium is a dynamic process that is tightly controlled at a local level to ensure safe and rapid repair with minimal loss of structure and function. The mechanisms controlling this process are not clear, and further research in this important area is required.

Authors contribution

R.G.: designed the study, provided specimens and wrote the manuscript; R.H., K.A.K. and C.B.: collected material and images and contributed to study.

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