Endometrial lysosomal enzyme activity in ovulatory dysfunctional uterine bleeding, IUCD users and post-partum women

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The aim of this study was to evaluate the role of lysosomal enzymes in excessively heavy menstruation by comparing women with menorrhagia due to dysfunctional bleeding or intrauterine contraceptive device (IUCD) use with those with normal menstrual periods or with amenorrhoea associated with breastfeeding. This was a prospective cohort investigation of the activity of four endometrial lysosomal enzymes in three contrasting groups: (i) women with ovulatory dysfunctional uterine bleeding and users of intrauterine contraceptive devices; (ii) breastfeeding post-partum women in whom there are long periods of amenorrhoea, particularly in the early months post-partum; and (iii) normal cycling women. It was found that the total activity of lysosomal enzymes, particularly acid phosphatase and N-acetyl-β-D-glucosaminidase, was markedly elevated (P < 0.001) in IUCD-exposed endometrium, and endometrium from women with dysfunctional uterine bleeding when compared with endometrium from women with a history of entirely normal menstrual periods or that in post-partum breastfeeding women. The activity of α-L-fucosidase was moderately elevated in IUCD users (P < 0.05) and ovulatory dysfunctional uterine bleeding (P < 0.05), whereas α-D-mannosidase activity was elevated in ovulatory dysfunctional uterine bleeding (P < 0.05), but decreased in IUCD users (P < 0.01). No significant differences were observed in the lysosomal enzyme activities of breastfeeding post-partum women and normal cycling women. These results show that total endometrial tissue activity of four lysosomal enzymes was substantially increased throughout the cycle in most circumstances in women with two different causes for increased menstrual bleeding. This suggests a contributory role to the increased bleeding.

Key words: endometrium/intrauterine contraceptive devices/lysosomal enzymes/menorrhagia/post-partum endometrium

Introduction

Lysosomes are heterogeneous intracellular vacuoles containing a wide variety of acid hydrolases. They are involved in autophagy and heterophagy and are capable of multiple enzyme release; these functions are crucial to tissue remodelling (DeDuve and Wattiaux, 1966). It has been proposed that lysosomal autophagy, heterophagy and the progressive accumulation and release of lysosomal enzymes may be an important mechanism leading to endometrial bleeding, remodelling and subsequent regeneration (Henzl et al., 1972; Wang and Fraser, 1989).

There is still much uncertainty about the complex molecular and pathophysiological mechanisms of menorrhagia in women with ovulatory dysfunctional uterine bleeding (Fraser et al., 1996). Numerous regulatory molecules such as increased endometrial fibrinolytic activity, decreased endothelins, altered expression of matrix metalloproteinases, apoptosis, altered leukocyte numbers and function and cytokine expression have been implicated (Smith et al., 1981; Fraser et al., 1996; Tabibzadeh, 1996). They may also affect lysosomal enzymes indirectly (Henzl et al., 1972), however, there is no published information on the behaviour of endometrial lysosomes and their enzymes in women with ovulatory dysfunctional bleeding.

It has been well demonstrated in the literature that women using small copper bearing intrauterine contraceptive devices (IUCD) experience increased menstrual blood loss by 50–75% (Larsson et al., 1975; Liedholm et al., 1975; Milson et al., 1989). The presence of an IUCD is associated with a foreign-body reaction consisting of migratory leukocyte infiltration in the endometrium especially at the sites of contact with the IUCD (Baron and Esterly, 1975). Histochemical studies have demonstrated that these mononuclear cells contained more lysosomes than resident cells of normal secretory endometrium (Baron and Esterly, 1975). Two biochemical studies have reported increased activities of endometrial lysosomal enzymes throughout IUCD-exposed cycles (Hagenfeldt et al., 1977; Mercado et al., 1984).

In contrast to dysfunctional uterine bleeding and IUCD
exposure, breastfeeding in the post-partum period maintains a ‘static’ state in the endocrine profiles and the histology of the endometrium (Topkin, 1943; Udesky, 1950). Most lactating women exhibit ‘atrophic’ or minimally proliferative endometrium (Topkin, 1943; Sharman, 1966; El-Minawi and Foda, 1971). It is thought that ‘the stationary or static nature of the endometrium in lactational amenorrhoea... is impressive and would seem to imply neither maturation nor regression of the ovarian follicles, but rather a state of follicular stasis’ (Udesky, 1950). Little is known about endometrial lysosomal activity in this situation. What is known is that breastfeeding is associated with prolonged amenorrhoea and rarely breakthrough bleeding (Wang and Fraser, 1994). Investigation of the ‘static’ nature of post-partum endometrium may provide a contrast for the role of lysosomal enzymes in cyclical menstrual bleeding and its abnormalities.

Menorrhagia involves a complex interplay of molecular and biochemical pathways. The authors believe that endometrial lysosomes and their enzymes have a role in this complex mechanism. Although lysosomal functions are multifaceted, the aim of this study was to establish a possible role for lysosomal enzymes in endometrial bleeding by studying one aspect of lysosomal function: namely, the biochemical measurement of total endometrial tissue lysosomal enzyme activity. Enzyme activity was measured under three contrasting situations; (i) regular menstrual cycling; (ii) excessive menstrual bleeding due to dysfunctional uterine bleeding or IUCD exposure; and (iii) breastfeeding influenced ‘static’ and ‘stable’ post-partum endometrium. The four enzymes studied were acid phosphatase, N-acetyl-β-D-glucosaminidase, α-L-fucosidase and α-D-mannosidase.

Materials and methods

Clinical recruitment

Normal subjects
Patients were recruited if they were aged 20–45 years with subjective report of entirely normal menstrual cycles, not on recent hormonal treatment, attending the operating theatre mainly for laparoscopic sterilization or treatment for low grade cervical intra-epithelial neoplasia. These results have been analysed and reported previously (Wang et al., 1999).

Women with ovulatory dysfunctional uterine bleeding
Patients were recruited if they were aged 20–45 years, not receiving recent hormonal treatment and undergoing hysteroscopy and dilatation and curettage for investigation of a clinically convincing history of menorrhagia on detailed questioning (Fraser, 1989).

IUCD users
Patients were recruited if they were aged 20–45 years, using a copper-bearing IUCD, not on recent hormonal treatment and attending the operating theatre for removal or change of IUCD. Most gave a history of some increase in menstrual loss, but only sometimes regarded this as excessive.

Post-partum breastfeeding women
A total of 67 women aged 20–45 years who were planning to breastfeed were recruited in the first post-partum week. Biopsies were taken at the first post-natal visit when initial bleeding had ceased. A second and third biopsy were planned, although not always achieved. These were labelled post-partum 1 (days 35–60 post-partum), post-partum 2 (days 61–120 post-partum) and post-partum 3 (days 121–210 post-partum). At the time of all these biopsies, the mothers were fully or partially breastfeeding. Menses had returned in all cases by the third biopsy.

In all cases, informed consent was obtained. The study was approved by the Ethics Review Committee of the Central Sydney Area Health Service. The endometrial biopsy or first strip of the endometrium at dilatation and curettage was collected with care to avoid contamination with vaginal fluid. The tissue was passed immediately to a research assistant for processing. Day of menstrual cycle was accurately documented and a portion of the endometrium sent for precise blinded histological staging. Samples were treated and assayed as described and validated previously (Wang et al., 1999).

Enzyme assay and DNA determination

Enzyme assays were performed with enzyme-specific substrates containing the 4-methyl umbelliferone (4MU) fluorophores as previously described (Wang et al., 1999). DNA measurement was carried out using Compound Hoechst 33258 (2-[2-(4-hydroxyphenyl)-6-benzimidazolyl]-6-(1-methyl-4-piperazyl)-benzimidazolo3HCl) (American Hoechst Co, Behring Diagnostic, La Jolla, CA, USA) as previously described (Wang et al., 1999).

Calculations and statistical analysis

Total tissue concentrations of enzymes and DNA were calculated firstly by obtaining a standard curve by regression analysis and expressed as activity (µIU) over DNA content (µIU/µg DNA) as previously described (Wang et al., 1999).

The data in this study were not normally distributed and a logarithmic transformation was applied before analysis. Comparisons were made of enzyme activity between groups using the F-test after logarithmic transformation.

Results

A total of 45 endometrial biopsies were obtained from normal subjects; three in the menstrual phase, 21 in the proliferative and 21 in the secretory phase (Wang et al. 1999). In all, 26 endometrial biopsies were obtained from the IUCD users; two in the menstrual phase, 12 in the proliferative phase and 12 in the secretory phase. A total of 23 biopsies were obtained from women with ovulatory dysfunctional bleeding; two in the menstrual phase, 12 in the proliferative and nine in the secretory phase.

Whilst most post-partum women happily participated in the initial post-partum biopsy usually scheduled at their 6 week postnatal visits, they found it increasingly difficult to return for repeat biopsies with the demand of travelling some distance with a new baby. Drop-out rate was high in these women, and only 12 women were able to continue through to the third biopsy. In practice, biopsies also became more difficult to obtain with time as the uterus decreased in size and the cervical os closed more tightly during lactational involution. At the third biopsies, adequate samples could not be obtained in four women because the cervical os was tightly closed. In a study period of 2 years, 12 post-partum women were successfully biopsied three times each over 30 weeks post-partum. Samples (n = 67) of adequate volume were analysed from post-partum group 1 (days 35–60), 22 from post-partum group 2 (days 61–120) and 12 from post-partum group 3 (days 121–210).

The results of all four enzymes for all four study groups
Table I. Total endometrial tissue activity (median and range) of lysosomal enzymes (µIU/µg DNA) for all six groups. Values in parentheses show the range of concentrations.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Normal (n = 45)</th>
<th>IUCD (n = 26)</th>
<th>DUB (n = 23)</th>
<th>PP1 (n = 67)</th>
<th>PP2 (n = 22)</th>
<th>PP3 (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP</td>
<td>2.5 (0.5–17.9)</td>
<td>12.4 (0.5–61.3)</td>
<td>11.3 (1.0–61.0)</td>
<td>2.0 (0.5–18.7)</td>
<td>2.1 (0.6–9.3)</td>
<td>1.2 (0.4–7.4)</td>
</tr>
<tr>
<td>FUC</td>
<td>0.06 (0.008–0.7)</td>
<td>0.1 (0.001–1.2)</td>
<td>0.2 (0.03–0.5)</td>
<td>0.06 (0.03–0.9)</td>
<td>0.08 (0.006–0.3)</td>
<td>0.05 (0.01–0.4)</td>
</tr>
<tr>
<td>GLU</td>
<td>1.3 (0.02–10.5)</td>
<td>9.3 (0.2–45.6)</td>
<td>9.0 (0.2–45.6)</td>
<td>1.4 (0.8–21.7)</td>
<td>1.2 (0.1–11.3)</td>
<td>2.9 (0.2–15.5)</td>
</tr>
<tr>
<td>MAN</td>
<td>0.03 (0.003–0.4)</td>
<td>0.01 (0.002–0.2)</td>
<td>0.09 (0.01–0.5)</td>
<td>0.02 (0.004–0.3)</td>
<td>0.05 (0.003–0.4)</td>
<td>0.02 (0.01–0.2)</td>
</tr>
</tbody>
</table>

Normal = normal subjects; IUCD = IUCD users; DUB = women with ovulatory dysfunctional bleeding; PP1 = Post-partum 1 (days 35–60 post-partum); PP2 = Post-partum 2 (days 61–120 post-partum); PP3 = Post-partum 3 (days 121–210 post-partum). ACP = acid phosphatase; FUC = α-L-fucosidase; GLU = N-acetyl-β-D-glucosaminidase; MAN = α-L-mannosidase.

Figure 1. Box whisker plot of logarithmically transformed acid phosphatase activity log(µIU/µg DNA) for normal subjects (Normal), intrauterine contraceptive device (IUCD) users, women with dysfunctional bleeding (DUB), breastfeeding women during days 35–60 post-partum (Post-partum 1), breastfeeding women during days 61–120 post-partum (Post-partum 2) and those during days 120–210 post-partum (Post-partum 3). *IUCD group was significantly higher (P < 0.001) compared with the normal and post-partum groups, but comparable with the DUB group. †DUB group was significantly higher (P < 0.001) compared with the normal and post-partum groups, but comparable with the IUCD group. Post-partum 3 group was significantly lower (P < 0.01) compared with all other groups.

Figure 2. Box whisker plot of logarithmically transformed α-L-fucosidase activity log(µIU/µg DNA) for normal subjects (Normal), IUCD users (IUCD), women with dysfunctional bleeding (DUB), breastfeeding women during days 35–60 post-partum (Post-partum 1), breastfeeding women during days 61–120 post-partum (Post-partum 2) and those during days 120–210 post-partum (Post-partum 3). *IUCD group was significantly higher (P < 0.05) compared with the normal and post-partum groups, but comparable with the DUB group. †DUB group was significantly higher (P < 0.05) compared with the normal and post-partum groups, but comparable with the IUCD group.

All three enzymes did not vary significantly from the proliferative, to the secretory or the menstrual phase with IUCD use. α-D-mannosidase activity was significantly lower (P < 0.01) in the IUCD-exposed endometrium than in normal subjects (Figure 4). This change was also observed throughout the menstrual cycle.

Lysosomal enzymes in women with ovulatory dysfunctional menstrual bleeding and comparison with normal subjects

In women with ovulatory dysfunctional bleeding, both acid phosphatase and N-acetyl β-D-glucosaminidase activities were significantly greater (P < 0.001) than normal subjects (Table...
2) and those during days 120–(Normal), intrauterine contraceptive device (IUCD), Discussion (Figures 1, 2, 3 and 4). The increased activity was seen secretory phase. fi were significantly lower (P < 0.01) than all other groups. †DUB group was significantly higher (P < 0.001) compared with the normal and post-partum groups, but comparable with the DUB group. *IUCD group was significantly higher (P < 0.001) compared with the normal and post-partum groups, but comparable with the IUCD group. While the differences were recorded in the total enzyme activity for α-L-fucosidase, α-d-mannosidase, N-acetyl-β-D-glucosaminidase in any of the post-partum groups over the three time frames studied (Figures 2, 3, and 4).

Comparison between IUCD use and ovulatory dysfunctional uterine bleeding

When compared with the dysfunctional uterine bleeding group, α-d-mannosidase in the IUCD group was low (P < 0.01). All the other three enzymes were comparable between IUCD users and women with dysfunctional bleeding (Figures 1, 2, 3 and 4).

Lysosomal enzymes in post-partum endometrium

Acid phosphatase activity showed a decrease from the second to the third biopsy; the first two biopsies were not statistically different, but the third biopsy showed results statistically lower than the other two groups (P < 0.01) (Figure 1). No statistical differences were recorded in the total enzyme activity for α-L-fucosidase, α-d-mannosidase, N-acetyl-β-D-glucosaminidase in any of the post-partum groups over the three time frames studied (Figures 2, 3, and 4).

Trend analysis for changes in lysosomal enzymes over time in post-partum endometrium

For the 12 volunteers who had three consecutive biopsies over the post-partum period of weeks 5–30, median values were calculated and results were analysed separately with analysis of variance to examine possible trends of enzyme activity over time. No significant trend could be observed (Table II).

Discussion

This appears to be the first demonstration that endometrial lysosomal enzyme activity is disturbed in women with ovulatory dysfunctional uterine bleeding. This is also the first study which examined lysosomal enzyme activity in post-partum endometrium beyond the first post-partum month.

All four enzymes studied showed significantly higher activity in women with dysfunctional bleeding than normal subjects. The increase was observed throughout the menstrual cycle. No differences were found between the proliferative and the secretory phase.

### Table II. Total endometrial lysosomal enzyme activities for 12 post-partum women with serial biopsies (µIU/µg DNA). Values in parentheses show the range of concentrations

<table>
<thead>
<tr>
<th>Enzyme median (µIU/µg DNA)</th>
<th>Post-partum 1</th>
<th>Post-partum 2</th>
<th>Post-partum 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP</td>
<td>2.3</td>
<td>2.4</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>(0.5–12.0)</td>
<td>(1.1–5.7)</td>
<td>(0.4–7.4)</td>
</tr>
<tr>
<td>FUC</td>
<td>0.1</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(0.04–0.5)</td>
<td>(0.04–0.3)</td>
<td>(0.01–0.4)</td>
</tr>
<tr>
<td>GLC</td>
<td>2.2</td>
<td>1.2</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>(0.1–11.0)</td>
<td>(0.6–4.8)</td>
<td>(0.2–15.5)</td>
</tr>
<tr>
<td>MAN</td>
<td>0.04</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(0.02–0.1)</td>
<td>(0.02–0.4)</td>
<td>(0.01–0.2)</td>
</tr>
</tbody>
</table>

ACP = acid phosphatase; FUC = α-L-fucosidase; GLC = N-acetyl-β-D-glucosaminidase; MAN = α-L-mannosidase.
In IUCD-exposed endometrium, activity of three lysosomal enzymes (acid phosphatase, N-acetyl-β-D-glucosaminidase and \( \alpha \)-l-fucosidase) was significantly higher than in normal endometrium. The increased enzyme activity associated with IUCD use was observed throughout the cycle with no significant changes from the proliferative to the secretory phase in the same manner as ovulatory dysfunctional uterine bleeding. \( \alpha \)-D-mannosidase activity was significantly lower than in normal endometrium. This was out of synchrony with the changes that were found for other enzymes. It is not clear why \( \alpha \)-D-mannosidase activity should be reduced significantly below normal in the presence of an IUCD. It is also uncertain whether IUCD-exposed endometrium has decreased requirements for \( \alpha \)-D-mannosidase or whether a low \( \alpha \)-D-mannosidase concentration could be attributed to a different population of endometrial lysosomes, and indeed whether this has any relevance to heavy menstrual bleeding in women. Nevertheless, endometrial lysosomal activity in three out of four of the enzymes studied was significantly increased in the presence of an IUCD, a result which is in agreement with previous studies (Hagenfeldt et al., 1977; Mercado et al., 1984).

It is of interest to note that the endometrial lysosomal enzymes (except mannosidase) in both the IUCD and the dysfunctional uterine bleeding groups showed parallel results reflecting the clinical manifestation of increased menstrual loss in both groups.

Lysosomes and their enzymes have long been implicated in normal menstrual bleeding (Henzl et al., 1972; Wang and Fraser, 1989). In normal physiological processes, endometrial lysosomes are thought to be active in autophagy and heterophagy to facilitate tissue re-modelling (Ferenczy, 1976). As such, total amounts of lysosomal enzyme in tissue are unlikely to be altered in most normal physiological processes. It is thought that the withdrawal of oestrogen and progesterone causes activation of the endometrial lysosomal system and release of their hydrolytic enzymes resulting in cellular digestion (Henzl et al., 1972). This release may be complete or it may be a process of slow leakage brought about by changes in lysosomal membrane permeability consequent upon changes in steroidal hormonal concentrations (Szego, 1974).

In the IUCD-exposed endometrium, endometrial reaction against a foreign body stimulates an inflammatory response which is probably the key to a series of biochemical events leading to excessive menstrual bleeding. This foreign body reaction involves the infiltration of migratory leukocytes which may influence tissue damage, repair and regeneration. Part of this process may involve an exaggerated synthesis and later activation of lysosomes and their enzymes, an event not observed in normal physiological processes. These enzymes may be involved in glycoprotein metabolism and tissue breakdown contributing to heavy menstrual bleeding. Other subcellular events such as the activation of prostaglandin release, fibrinolytic pathways and migratory leukocytes are also likely to be important in IUCD-related menorrhagia.

It is not clear what mechanisms are responsible for an exaggerated lysosomal synthesis and activation in women with ovulatory dysfunctional uterine bleeding. The regulatory mechanisms for menstruation are complex and the interactions between different regulatory molecules are still poorly understood. Biochemical changes in endometrial phospholipases and arachidonic acid metabolism are evident in women with dysfunctional bleeding (Bonney and Franks, 1987; Bonney et al., 1991). Phospholipases are known lysosomal enzymes and this is consistent with an influence of lysosomal enzymes on prostaglandin pathways. Alternatively, it has also been suggested that lysosomes may be positively influenced by prostaglandin production and this effect may be exerted through the cyclic nucleotides (Goldfarb and Thomas, 1983). An exaggerated activation of prostaglandin pathways and fibrinolytic activity are thought to be important mechanisms in ovulatory dysfunctional uterine bleeding (Smith et al., 1981; Cameron, 1989). Lysosomes and their enzymes may be activated in ovulatory dysfunctional bleeding in a manner closely linked to the prostaglandins. The weight of evidence seems to suggest that endometrial lysosomes are involved in a remodelling role once tissue breakdown has started, and could contribute to the volume and duration of bleeding.

In addition to the activation of endometrial lysosomes, prostaglandins and fibrinolysis, it is thought that vasoconstriction and tissue ischaemia may activate multiple tissue molecules capable of tissue damage, shedding and subsequent repair and regeneration. These tissue molecules may include free oxygen radicals, matrix metallo-proteinases and their inhibitors, endothelium-derived relaxing factor (nitric oxide), platelet-activating factors, leukotrienes, interleukins, tumour necrosis factor, natural killer cells, lymphokine-activated killer cells, apoptosis mediators and a range of tissue growth factors (Fraser et al., 1996; Tabibzadeh, 1996).

It is possible that the activation of migratory leukocytes may play a central role in the release of these tissue molecules in ovulatory dysfunctional bleeding (Fraser et al., 1996), an event also observed in IUCD-exposed endometrium as a result of foreign body reaction. In a parallel study, blinded histological controls for all samples were obtained and detailed morphometric analyses were performed (Wang et al., 1995). The findings showed that endometrial total leukocyte infiltration was more abundant in women with ovulatory dysfunctional bleeding (median 41.4/1000 stromal cells) (\( P < 0.05 \)) although less so in users of IUCD (median 32.3/1000 stromal cells) (not significant) compared with normal subjects (median 30.1/1000 stromal cells). Nevertheless, IUCD use was associated with significant plasma cell infiltration (\( P < 0.05 \)) compared with normal cycling endometrium (Wang et al., 1995). It is therefore logical to speculate that endometrial lysosomes, prostaglandins and migratory leukocytes are closely linked. Unlike IUCD exposure, the original trigger for dysfunctional bleeding is unclear. Nevertheless, results from this study have indicated that lysosomes and their enzymes play a role in the complex interplay of metabolic events contributing to heavy menstrual bleeding often seen in both IUCD users and women with dysfunctional uterine bleeding.

Despite the influence of breastfeeding and prolonged periods of amenorrhoea, in post-partum endometrium where histology showed proliferation, lysosomal enzyme activity was very similar to that in normal endometrium (both the proliferative and secretory phase) and there was no general increasing or
decreasing trend with time. Enzyme activities were fairly stable from days 35–210 post-partum in parallel with observed ‘static’ morphology under the influence of breastfeeding. Acid phosphatase showed a significant decrease in activity from the second to the third post-partum biopsies ($P < 0.01$), but this pattern was not repeated for the other enzymes. The results indicate that the post-partum endometrium in breastfeeding women provides a stable, but comparable ‘baseline’ model similar to normal cycling endometrium for the study of the role of endometrial lysosomal enzymes in other situations where lysosomes may be important, such as neoplasia, infection, hormonal influence or dysfunctional bleeding.

Acid phosphatase is a well known traditional marker of lysosomal activity. Together with N-acetyl-β-D-glucosaminidase, α-L-fucosidase and α-D-mannosidase, these enzymes are involved in glycoprotein, glycolipid and mucopolysaccharide metabolism, but their exact role in the human endometrium is unclear. N-acetyl-β-D-glucosaminidase has been used as a modern marker of lysosomal activity and its concentration usually changes in parallel to that of acid phosphatase in the endometrium. The presence of α-L-fucosidase and α-D-mannosidase in the human endometrium has been confirmed previously (Cornillie et al., 1991). Their activities in normal endometrium were low and fluctuations minimal in contrast to acid phosphatase and N-acetyl-β-D-glucosaminidase, the activities of which were 10–100-fold higher. Whilst their exact functions in endometrium are unknown, it may be that endometrial α-L-fucosidase and α-D-mannosidase are triggered in different but yet unidentified circumstances compared with the other two enzymes.

It may be speculated that other lysosomal enzymes which were not measured in this study may play a more important role in endometrial bleeding than the four enzymes studied. However, these findings indicate that there is a significant disturbance of overall lysosomal enzyme function in menorrhagia due to ovulatory dysfunctional uterine bleeding or IUCD use. Whilst the metabolic interplay leading to menstrual bleeding is complex and the interactions amongst different mediators are still poorly understood, endometrial lysosomes and their enzymes may be important mediators in some pathways associated with menorrhagia.

References


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Lyosomal enzymes in endometrial bleeding