Endometrial thickness measured by ultrasound scan in women with uterine outlet obstruction due to intrauterine or upper cervical adhesions

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BACKGROUND: A subgroup of women with Asherman’s syndrome has adhesions of limited extent completely blocking the lower uterine cavity or upper cervix, whereas the upper endometrium remains normal. Haematometra are rarely found in these women. We tested the hypothesis that women with localized adhesions occluding the uterine outlet (but not affecting the upper uterine cavity) will have much thinner endometrium than controls. METHODS: Twenty-six women with Asherman’s syndrome (16 with limited outlet adhesions only) and 50 with normal menstrual cycles underwent transvaginal ultrasound scan where endometrial double thickness was measured precisely and the cycle phase assessed. The presence of any fluid in the uterine cavity was noted. RESULTS: The endometrium in women with Asherman’s syndrome, in whom uterine outlet blockage was the sole abnormality (subgroup 3), was substantially thinner (mean ± SEM: 3.9 ± 0.4 mm) than controls (8.5 ± 0.05; P < 0.001), and haematometra were very uncommon (1 of 16). Endometrial thickness at all stages of the ovarian/menstrual cycle in all three subgroups of Asherman’s syndrome was significantly less than in normal menstruating controls. CONCLUSIONS: Non-invasive ultrasound measurements have demonstrated very thin endometrium and absence of haematometra in most women with uterine outlet occlusion by adhesions. This unusual phenomenon of failure of cyclical endometrial growth and breakdown in the sole presence of cervical occlusion by adhesions merits further study.

Keywords: endometrium; ultrasound; intrauterine adhesions; Asherman’s syndrome

Introduction

Asherman’s syndrome was first described by Fritsch (1894) but it was Asherman who first pointed out the frequency of the pathologic condition and described the symptoms of amenorrhoea, infertility and dysmenorrhoea following complicated delivery or abortion (Asherman, 1948). Although amenorrhoea is common in this syndrome, many women have adhesions of limited extent and little or no reduction in the menstrual flow.

The main cause of this syndrome is the procedure of endometrial curettage required to treat secondary postpartum haemorrhage due to retained placental products (Westendorp et al., 1998). In this situation, the myometrium is softened by the pregnancy and often by an accompanying low-grade infectious process. The traumatizing effect of a sharp curette contributes to the likelihood that a full depth of endometrium will be removed (Foix et al., 1966). When the basal layer of endometrium and some underlying myometrium are removed, which is a common pathological finding in postpartum curettage specimens, there is predisposition to the formation of intrauterine and cervical adhesions. The apposed myometrial surfaces adhere and allow irregularly shaped, dense and mature fibrous adhesions to form.

It has also been suggested that missed abortions are an important risk factor for the development of adhesions. Placental remnants and villous elements may promote fibroblastic activity and collagen formation before endometrial regeneration has taken place, leading to scarring and menstrual disturbances (Schenker, 1996). An incidence of around 18% was found for the development of intrauterine adhesions after missed abortions (Golan et al., 1992; Friedler et al., 1993). In another prospective study, the prevalence of intrauterine adhesions among women undergoing secondary removal of placental remnants after delivery or repeat curettage for incomplete abortion was found to be 40%. (Westendorp et al., 1998).
In the very specific situation of suction termination of first trimester pregnancy using a disposable curette with sharp recurved edges, there may be localized damage to the region of the internal os, leading to the development of a dense sheet of adhesions occluding the uterine outlet (Fraser et al., 1995). These adhesions may vary from a few millimetres to 1–2 centimetres thick. The endometrium above these adhesions is usually entirely normal, but appears to become relatively unresponsive to hormonal stimulation (Asherman, 1948; Toaff and Ballas, 1978).

Since the early 1990s, hysteroscopy guided by transrectal ultrasound has provided greatly increased precision for division of intrauterine adhesions in patients with Asherman’s syndrome (Fraser et al., 1995). In women in whom the outflow of the uterus is completely blocked by adhesions, there is a clinical impression that the endometrium assessed by curettage is thinner than expected for the stage of the ovarian cycle and that it is uncommon for a haematometra to be encountered (Asherman, 1948; Toaff and Ballas, 1978; Polter et al., 2006). Histology has also sometimes indicated a ‘quietscent’ or atrophic endometrium (Asherman, 1948). Although Asherman and others have suggested that the endometrium becomes unresponsive when outlet adhesions are present, there is remarkably little objective evidence to support this.

The lack of haematometra with upper cervical occlusion is in contrast to other types of lower genital tract occlusion such as transverse vaginal septa, imperforate hymen, partial vaginal agenesis and even occlusion at the external os, which also result in symptoms of amenorrhoea and sometimes dysmenorrhoea. However, haematometra, haematoocolpos and haemato- rhoea are almost always found in these cases. Taken together, these observations may be interpreted to mean that the localized outlet-occluding cervical adhesions (at the internal os) of this type of Asherman’s syndrome may have a local effect limiting the growth and breakdown of normal endometrium. Possible mechanisms are unknown.

Although regular ovulation continues in women with Asherman’s syndrome, it seems that in women with extensive adhesions the endometrium does not react to the hormonal cycle or hormone therapy and the endometrium remains in a state of relative inactivity. Asherman called this the ‘ovulating non-bleeding’ phenomenon. However, after division of the adhesions, menstruation returns towards normal (Fraser et al., 1995; Schenker, 1996; Polter et al., 2006) and pregnancy can occur. Menstruation may not be of the same volume and duration as previously, depending on the extent of adhesions (Asherman, 1948). Foix et al. (1966) found that 80.6% of the total group of patients recovered their normal menses, but only 54.5% of the women with significant intracavitary adhesions achieved eumenorrhoea. This percentage increased to 92.4% for women who only had upper cervical adhesions.

We set out to test the hypothesis that women with localized adhesions occluding the uterine outlet (but not affecting the upper uterine cavity) will have much thinner endometrium, as measured by transvaginal ultrasound, than women at the equivalent stage of the normal menstrual cycle. We also hypothesized that we would rarely encounter ultrasound evidence of a haematometra in these women.

Materials and Methods

A case series of 26 women with the diagnosis of Asherman’s syndrome (mean age ± SD at ultrasound scan, 30.8 ± 6.0, range 20–43 years), who attended a single specialist reproductive endocrine clinic during the last 20 years, were identified from case records. This study was approved by the Human Research Ethics Committee of the University of Sydney. Data on endometrial thickness (ET) in this group with Asherman’s syndrome were obtained by review of detailed diagnostic transvaginal ultrasound scans carried out by one specialist pelvic ultrasound group during the investigation of these patients over a 20 year period. None of the women used hormonal contraception or other medication(s) which may have affected the uterus. The menstrual cycle phase [proliferative (n = 14) or secretory (n = 5) or atrophic endometrial appearance (n = 7)] was determined in all the ultrasound scans by endometrial appearance by a specialist in gynaecological ultrasonography. Ovarian assessment by transvaginal ultrasound scan was also carried out to determine continuing ovarian cyclical activity. All women also underwent later hysteroscopy, division of adhesions, endometrial sampling and menstrual cycle follow-up.

The ET of women with Asherman’s syndrome was compared with a historical control group studied using identical technique (Baerwald and Pierson, 2004). In the control study, ET was measured daily through the menstrual cycle using repeated transvaginal ultrasonography. All participants (n = 50, mean age ± SD, 28.0 ± 6.9, range 19–43 years) were in good health and had previous regular menstrual cycles with duration of 26–32 days (mean 28 days). None was using hormonal contraception within 3 months of enrolling or taking medication(s) known or suspected to interfere with reproductive function. These women were fertile volunteers who agreed to have ultrasound measurements of the endometrium every 1–2 days through one menstrual cycle. None had a previous history of irregular menstrual cycles, systemic diseases or previous surgery in the pelvis, or had symptoms or signs of any condition that could interfere with normal development of the endometrium. In the proliferative phase, 501 measurements of the ET were taken with ultrasound, and 649 measurements in the secretory phase (Baerwald and Pierson, 2004).

There are several published classifications of the extent of intrauterine adhesions, including the European Society for Hysteroscopy (Wamsteker and De Block, 1993) and the American Fertility Society Classification of Intra-Uterine Adhesions (American Fertility Society, 1988). Whereas the former describes the extent of intrauterine adhesions, the latter uses a point counting system for the extent of cavity involved, type of adhesions and menstrual pattern. However, none of the classification systems distinguishes intrauterine adhesions from endocervical adhesions. Therefore, in the present study, a modified classification was used in order to define the level of adhesions:

(i) Subgroup 1 included women with severe intrauterine adhesions; the tubal ostia were not visible on hysteroscopy and over 50% of the uterine cavity was obliterated by adhesions.
(ii) Subgroup 2 included women with moderate/mild intrauterine adhesions; 1 or both tubal ostia were seen on hysteroscopy and less than 50% of the uterine cavity was obliterated by adhesions.
(iii) Subgroup 3 included women with cervical or limited lower uterine cavity adhesions only. These women developed adhesions solely following vacuum curettage for termination of pregnancy or for spontaneous abortion.
Statistics

The analysis was divided into two parts in relation to the phase in the menstrual cycle. Data on ET were compared between the Asherman’s syndrome and control groups and among the subgroups and control group. For the proliferative phase, the independent samples t-test was used for the statistical analysis of ET between the Asherman’s and control groups. For comparison between subgroups, the ANOVA test was used. Particular emphasis was directed to subgroup 3. ANOVA with contrast was used to compare subgroup 3 with controls. This is used to demonstrate where the significant differences lie in the groups being compared by ANOVA.

For the secretory phase, the Mann–Whitney test was used for both comparison between the ET in the Asherman’s syndrome versus control group and the analysis for subgroup 3 versus control. P-value of <0.05 was taken to indicate a statistically significant difference for each analysis.

Results

A total of 26 transvaginal ultrasonographic images (one per woman) of the uterus and ovaries were studied in women with Asherman’s syndrome; 14 were in the proliferative and 5 in the secretory phases, and 7 were described as ‘atrophic’ endometrium and could not be definitely categorized to a stage of the cycle. Three of these seven women had a single ovarian follicle of at least 10 mm diameter, and one had a hae-morrhagic ovarian cystic structure consistent with a corpus luteum. The primary study group (subgroup 3) comprised 16 women with limited extent adhesions completely blocking the lower part of the uterine cavity or upper cervix. None of these women had adhesions thicker than 1 cm, and the endometrium in the body of the uterus was not directly affected by adhesions or scarring.

In the total Asherman’s syndrome group, the mean (± SEM) ET was 4.1 ± 0.4 mm. Compared to controls (8.5 ± 0.05 mm), ET in the Asherman’s syndrome group was highly significantly thinner (t = −7.2, df = 513, P < 0.001) (Table I). We were specifically interested in subgroup 3, with upper cervical or lower uterine cavity adhesions alone, where a highly significantly thinner ET was found in the proliferative phase (4.2 ± 0.5; P < 0.001 in subgroup 3 versus 7.2 ± 0.07 in controls). No analysis could be performed due to lack of power in subgroup 1, but significantly thinner endometrium compared with controls was also seen in the proliferative phase in subgroup 2 (3.1 ± 0.6; P < 0.001). It is of interest that the ET in women in subgroup 3, where the endometrium in the body of the uterus was undamaged, was no greater than in subgroups 1 and 2 where there was significant endometrial damage and adhesion formation.

A highly significant difference was also found in the secretory phase (z = −3.9, P < 0.001) between Asherman’s syndrome and control groups (mean ± SEM was 5.7 ± 0.8 mm and 9.5 ± 0.02, respectively). In the subgroup analysis, differences were less obvious compared with the proliferative phase, but were observed in groups 1 and 2 (z = −2.45, P < 0.05 in both groups) and not in group 3 (where n = 1) versus control (z = −1.7, P > 0.05).

Detailed scans were performed to determine the presence of fluid in the uterine cavity (haematometra) in all cases and fluid was only recorded in 1 out of 16 ultrasound scans in subgroup 3. In this single case, a fluid volume of 6 ml with the characteristics of blood was noted. In all the subjects in subgroup 3, later hysteroscopy confirmed limited adhesions, a normal uterine cavity and normal endometrial surface. Menstruation returned after hysteroscopic division of the outlet adhesions. A study of subsequent changes in ET was not undertaken following division of adhesions.

Discussion

ET measured by transvaginal ultrasonography is significantly decreased at all phases of the menstrual cycle in patients with Asherman’s syndrome compared with the ET in healthy menstruating women, supporting our principal hypothesis. In the secretory phase, significant differences were observed between the Asherman’s and control groups, but due to small sample size (n = 2 in subgroup 1, n = 2 in subgroup 2, n = 1 in subgroup 3), the validity of the observations in the secretory phase is questionable. Future analysis with higher numbers of patients in the secretory phase will be important to validate the data.

We were particularly interested in changes in ET in women who only had uterine outflow blockage and where the major area of endometrium was entirely normal (Toaff and Ballas, 1978). In these women, the endometrium was significantly thinner than expected and a haematometra was only seen in 1 out of 16 cases. Normal appearance of the endometrial area of endometrium was entirely normal (Toaff and Ballas, 1978). In these women, the endometrium was significantly thinner than expected and a haematometra was only seen in 1 out of 16 cases. Normal appearance of the endometrial surface and uterine cavity in these women was confirmed at subsequent hysteroscopy, and normal menstruation returned after division of the outlet adhesions.

It was expected that the endometrium would be significantly thinner in women with intrauterine adhesions and endometrial damage, but the observation that the endometrium was so much thinner in those women who had outlet adhesions alone (subgroup 3) was unanticipated. In these women, the endometrium

| Table I. Endometrial double-thickness measurements by transvaginal ultrasound in 26 women with Asherman’s syndrome (AS) and 50 controls. |
|---|---|---|---|
| ET of total AS group | 26 | 4.1 | 0.4 |
| ET in subgroup 3 | 16 | 3.9 | 0.4 |
| ET in control group* | 50 | 8.5 | 0.05 |
| Proliferative phase | | | |
| ET in AS group | 14 | 4.0 | 1.6 | <0.001 |
| ET in subgroup 3 | 11 | 4.2 | 0.5 | <0.001 |
| ET in subgroup 1 | 0 | — | — |
| ET in subgroup 2 | 3 | 3.1 | 0.6 | <0.001 |
| ET in control group* | 50 | 7.2 | 0.07 |
| Secretory phase | | | |
| ET in AS group | 5 | 5.7 | 0.8 | <0.001 |
| ET in subgroup 3 | 1 | 5.1 | — | NS |
| ET in subgroup 1 | 2 | 5.6 | 1.5 | <0.05 |
| ET in subgroup 2 | 2 | 6.2 | 2.1 | <0.05 |
| ET in control group* | 50 | 9.5 | 0.02 |
| ‘Atrophic’ subgroup 3 alone | 7 | 2.7 | 0.3 | <0.001 |

n, number of patients; ET, endometrial thickness; NS, not significant; P-value shows statistical comparison with the control group in that cycle phase or in the total Group. Subgroup 1, severe intra-uterine adhesions; Subgroup 2, moderate intrauterine adhesions; Subgroup 3, cervical adhesions only.

*Data recalculated from Baerwald and Pierson (2004).
was subsequently demonstrated to be ‘normal’, albeit thin, on histology at the time of hysteroscopy. In many of these subgroup 3 women, the endometrium and ovaries had ultrasound features consistent with the proliferative phase of the cycle but secretory phase endometrium and a corpus luteum were only noted in one. Seven others had very thin endometrium, classified as ‘atrophic’. Three of these only had small ovarian follicles and no corpus luteum, but three had one follicle of at least 10 mm and one had a haemorrhagic ovarian cyst consistent with a corpus luteum. It is not possible to exclude a small number of anovulatory cycles as contributing factors to this overall picture.

This study does not provide any clear indication of the mechanism whereby the endometrium in women with outlet adhesions would be so distinctly thinner than expected, although it can be hypothesised that there is inhibition of some aspect of the proliferation mechanism or activation of more rapid apoptosis.

The data presented in the present series provide strongly suggestive evidence that menstrual bleeding is inhibited when the outlet adhesions are present, although apparently normal menstruation returns when the adhesions have been divided. It is interesting to speculate that menstrual breakdown does occur at the appropriate stage of the cycle but that blood and fluid loss are somehow limited, or that resorption occurs rapidly. Rapid flow through the oviducts into the peritoneal cavity must also be a possibility. Rapid absorption seems unlikely when one considers that mean blood loss during one menstrual period is usually around 25–35 ml and that the total volume of menstrual fluid loss is double the blood loss (Fraser et al., 1985).

The absence of obvious haematometra (except in one case) is in stark contrast to the expectation of consistently large haematocolpos, haematometra and haematosalphinx in women with a vaginal transverse septum, imperforate hymen or adhesions occluding the external os. One can speculate that menstrual breakdown could be completely inhibited in some way by the presence of cervical and lower uterine adhesions through a local ‘feedback’ mechanism. Toaff and Ballas (1978) suggested some form of ‘visceral reflex’. However, it is perhaps more likely that there is only minimal bleeding at menstrual breakdown, since some of these women do experience cyclical pelvic cramps and one small haematometra was observed. It seems most probable that the primary disturbance in these women involves an inhibition of endometrial proliferation, or perhaps an exaggeration of apoptosis (Polter et al., 2006), demonstrated most obviously in the seven women (out of 16) in whom the endometrium was so thin as to be described as ‘atrophic’.

Tamura and colleagues (2006) studied the pathophysiology of unexpectedly thin endometrium in women with infertility focusing on uterine blood flow, growth of glandular epithelium, vascular development and angiogenic factors. The density of small blood vessels, the total area of glandular epithelium and the level of vascular endothelial growth factor (VEGF) expression were significantly lower in the thin endometrium compared with the group with normal endometrium. This could suggest that low blood flow is involved in the impairment of the growth of the glandular epithelium and stroma and in VEGF production leading to further poor angiogenesis and further reduction in uterine blood flow (Tamura et al., 2006).

It is not known whether the pathophysiology of the thin endometrium in women with Asherman’s syndrome could be due to similar, or to completely different, mechanisms. These mechanisms require further specific research on endometrium obtained from women with Asherman’s syndrome.

This case series has described an unexpected situation where an apparently normal endometrium has been effectively ‘switched off’ by the presence of a thin but dense band of adhesions occluding the uterine outlet. This observation raises interesting questions about mechanisms, with potential implications for exploration of new contraceptive techniques or enhancement of endometrial fertility mechanisms.

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References


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