

ELECTRON MICROSCOPIC STUDY OF THE UTERINE SEPTUM IN WOMEN WITH RECURRENT ABORTIONS

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ABSTRACT

Objective : To study the ultrastructure of the uterine septum in order to evaluate its role as a possible cause of pregnancy failure and to discuss the value of hysteroscopic metroplasty in women with recurrent spontaneous abortions.

Patients and methods : This investigation was carried out on 32 women with a history of recurrent abortions and with a proven septate uterus. They were diagnosed by hysterosalpingography, laparoscopy and/or hysteroscopy. The patients were subjected to hysteroscopic metroplasty and were followed-up for a period of 6 months to 3 years. Several Biopsies were taken during the proliferative phase from the upper, middle and lower parts of the uterine septum and from the lateral uterine wall for comparison. The specimens were processed for both scanning and transmission electron microscopic examination.

Results : Electron microscopic examination revealed defective preovulatory changes in the septal endometrium compared to the endometrium of the lateral uterine wall. These changes included reduced number of glandular orifices, irregular nonciliated cells with few or absent microvilli, incomplete ciliogenesis and reduced ciliated/nonciliated cell ratio. The uterine septum appeared as a very well-vascularized fibromuscular tissue. It contained numerous smooth muscle fibers separated by intercellular tissue containing collagen bundles that increased in amount in the lower part of the septum. Many capillaries and venules were present in the uterine septum. After hysteroscopic metroplasty, pregnancy occurred in 90% of the cases and 82.2% reached full term.

Conclusion : The classic concept of avascular fibrous septum is no longer acceptable as a possible cause of pregnancy failure. However, the ultrastructure of the septum, detected in the present study could explain the occurrence of recurrent abortion. Also, it is concluded that hysteroscopic metroplasty improves the obstetric performance of patients with recurrent abortions in terms of pregnancy continuation.

Key words : Septate uterus, recurrent abortion, electron microscopy.

INTRODUCTION

Septate uterus is the most common structural abnormality of all Mullerian duct defects (1,2). It results from incomplete resorption of the median septum formed by complete fusion of the two Mullerian ducts (3).

The incidence of the septate uterus is about 2-3% in the general population (4) and 35% of all

uterine anomalies (2,5). Regardless of its size, the septum is a significant risk factor for completion of pregnancy (6). Its presence is usually associated with poor reproductive performance including high incidence of first and second trimester abortion, and preterm delivery (7,8).

Several theories have been postulated to explain the association of high rates of recurrent spontaneous abortion with septate uterus. They

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have related the occurrence of abortion with a specific histological feature of the septum that causes abnormal placentation. March in 1983, reported that the septum is a fibroelastic tissue (9); while Fayez in 1986, reported that the septum has more connective tissue and fewer muscle fibers (10). Some investigators have claimed that the uterine septum is avascular (11,12). Others considered it as a poorly vascularized fibromuscular tissue (13).

Recently, the classic concept of avascular septum as a cause of pregnancy failure has been challenged. Sparac et al, described the intrauterine septum as a very well vascularized fibromuscular tissue (14). Surprisingly, most of the literature lacks extensive work on the histologic composition of the uterine septa. Therefore, it was the aim of the present investigation to document and evaluate the ultrastructure of the uterine septum, in women with a history of recurrent spontaneous abortions, using both the scanning and the transmission electron microscopes.

MATERIALS & METHODS

This clinical and histological investigation was carried out on 32 women with a history of three or more spontaneous successive abortions and with a proven septate uterus. They were diagnosed by hysterosalpingography, laparoscopy and/or hysteroscopy. These women were attending the Outpatient Clinic of Obstetrics and Gynecology, at Mansoura University Hospital, during the period from April 2000 to June 2003. After giving a written consent, the women were enrolled in this study. They were subjected to hysteroscopic metroplasty and were followed up for a period ranging from 6 months to 3 years. The decision to perform hysteroscopic metroplasty was based on the poor reproductive performance rather than the

presence of a septate uterus.

Hysteroscopic Metroplasty:

The procedure was performed during the proliferative phase of the menstrual cycle. All patients were under general anesthesia in the lithotomy position. A Hamou II microhysteroscope (Karl Storz, Germany) was introduced. After confirming the diagnosis, the 5 mm sheath was removed and the 9 mm one was inserted. The resectoscope with the cutting loop (diathermy knife) and the working element were introduced. The distending medium (1.5% glycine) was installed into the uterine cavity via a Hamou-Hysteromat (an electronically controlled irrigation delivery system that calculate the optimal pressure and the rate of flow of glycine). Several biopsies were taken and the septum was then excised using the diathermy knife of the resectoscope with a cutting current from 60-70 Watts. The lower half of the septum was cut from below upwards, while the upper half was cut from side to side in a shaving manner. The procedure was stopped 1 cm from the expected line connecting the tubal ostia to avoid fundal perforation.

With the hysteroscopic resection of the septum, a concurrent laparoscopy was done to confirm the diagnosis of septate and to reduce the risk of uterine perforation.

Postoperative conjugate estrogen and progesterone (1.25 mg and 10 mg/day, respectively) were prescribed for one month to assist epithelialization. Perioperative prophylactic antibiotic in the form of Doxycycline (100 mg twice daily) was given for one week. A postoperative follow-up examination was conducted after one month.

Ultrastructural Study:

Several biopsies were taken from the different levels of the septum, namely the upper part, the middle part and the lower part of the septum. A biopsy from the uterine wall was obtained from the lateral aspect of the uterine cavity for comparison.

all the specimens were immediately cut into very small pieces and were fixed in a freshly prepared cold 3% glutaraldehyde in 0.1 M phosphate buffer at 4°C for 2 hours. The specimens were then washed in cold phosphate buffer and postfixed with 1%ferrocyanide-reduced osmium tetroxide in 0.1M phosphate buffer at 4°C for 2 hours.

For the scanning electron microscopic study, the specimens were dehydrated in graded ethanol and critical point dried (15). The specimens were then coated with gold and examined with a JEOL T100 scanning electron microscope.

For the transmission electron microscopic study, the specimens were block stained overnight with 1% uranyl acetate in the refrigerator, dehydrated in graded ethanol and embedded in absolute Epon. Ultrathin sections with a gray interference color were cut, picked up on uncoated copper grids, double stained with uranyl acetate and lead citrate and examined with a JEOL 100 CX transmission electron microscope.

RESULTS

Clinical Data:

This investigation was conducted on 32 women with a history of recurrent abortions and proven septate uterus (Figs 1,2). The demographic data of the studied group are presented in Table I. The previous obstetric performance of the studied

group is presented in Table II. The follow-up periods of the cases following hysteroscopic metroplasty and their obstetric performance are shown in Table III.

Ultrastructural Study:

1. Scanning electron microscopy:

Examination of the surface of the endometrium of the lateral wall of the uterus (normal endometrium) during the proliferative phase of the menstrual cycle with the scanning electron microscope showed that the endometrial surface was highly folded and the ostia of numerous endometrial glands appeared scattered along the endometrial surface (Figs. 3-5). The endometrial surface appeared lined with small patches of ciliated cells interspersed with nonciliated secretory cells. The cilia appeared to be numerous, tall and vigorous. The nonciliated cells demonstrated convex apices covered with regularly distributed microvilli (Fig. 6).

On the other hand, the surface of the septal endometrium showed less number of uterine gland openings (Figs 4-7). The septal endometrial epithelium exhibited less number of ciliated cells and incomplete ciligenesis. The cilia appeared fewer and shorter. The nonciliated secretory cells were irregular and demonstrated few irregular microvilli (Fig. 8).

2. Transmission electron microscopy:

Transmission electron microscopic examination of the lateral wall of the uterus (normal endometrium) during the proliferative phase of the menstrual cycle (Figs. 9,10) showed that the endometrium was formed of a surface epithelium invaginated to form numerous tubular uterine glands and a thick lamina propria the endometrial stroma). The

surface epithelium appeared as a simple columnar epithelium that possessed scattered groups of ciliated and nonciliated secretory cells. The cilia were regular and markedly numerous. The apical cytoplasm of the ciliated cells contained plenty of mitochondria and many electron-dense lysosomes. The secretory cells contained widely dilated profiles of endoplasmic reticulum distended with electron-lucent or moderately electron-dense material (Fig. 9). variable-sized electron-dense lysosomes were also seen. The luminal surface of the secretory cells was provided with numerous regular microvilli (Fig. 9). The epithelium of the uterine glands was similar to the surface epithelium but the ciliated cells were fewer.

The septal endometrium (Figs. 11,12) exhibited less number of ciliated cells whose luminal borders were provided with few short cilia. The secretory cells were more numerous and demonstrated absent or few apical microvilli.

The uterine septal tissue showed varying degrees of a myometrial component composed of numerous spindle-shaped smooth muscle fibers with elongated vesicular nuclei (Figs. 13,14,15). The cytoplasm contained prominent longitudinally oriented microfilaments. The rest of the cell organelles tended to accumulate at the nuclear poles. The muscle fibers were separated by intercellular material containing collagen bundles. In the upper part of the septum (Fig. 13), the intercellular elements were little in amount and the muscle fibers were seen closely opposed to each other. In the middle part of the septum (Fig. 14), the intercellular material and the collagen bundles increased in amount. in the lower part of the septum (Fig. 15), the connective tissue elements were more abundant.

Numerous venules and blood capillaries were observed in the uterine septum (Fig.16). They were lined with thick endothelial cells with prominent nuclei and their lumina contained erythrocytes. The venules appeared partly surrounded with muscle fibers. The capillaries were either continuous or fenestrated and the nuclei of the associated pericytes were occasionally seen.

DISCUSSION

Septate uterus is associated with the highest incidence of reproductive failure and several obstetric complications. These complications include first and second trimester recurrent abortions and preterm delivery (16-18).

Approximately 15% to 25% of spontaneous recurrent abortions are thought to be caused by mullerian fusion defects, and almost all are associated with uterine septa (19). The mechanism by which the septate uterus causes pregnancy loss is not clearly understood. Abortions caused by the septate uterus is usually recurrent and has been attributed to implantation of the fertilized ovum in the septum which was suggested to have a poor blood supply leading to poor implantation or placentation and ending in inevitable abortion (20,21).

Hysteroscopic metroplasty has proved exceedingly successful and accumulated reports from different centers recommended its use as the first line in the treatment of women with a history of recurrent spontaneous abortions. The short operative time, the minimal postoperative morbidity and the avoidance of incision of the peritoneum made many investigators consider this technique as the line of choice in treatment of the intrauterine septum (14,22).

In the present study, the uterine septa were excised by hysteroscopic metroplasty with a follow-up period ranging from 6 months to three years. Pregnancy occurred in 28 out of 32 cases; a pregnancy rate of 90%. The pregnancy outcome was improved compared to that of the pretreatment state. Full term pregnancy was achieved in 23 women (82.2%). Two (7.1%) preterm deliveries and only 3 (10.7%) abortions were recorded. These findings support those of other investigators who evaluated the hysteroscopic treatment of different types of uterine septa and concluded that hysteroscopic metroplasty had improved the obstetric performance of the patients in terms of pregnancy continuation (2,22,23).

Histologically, it has been postulated for a long time that the uterine septum is formed of a fibroelastic tissue that is inadequately vascularized (9) or of connective tissue containing few muscle fibers (10,24).

In the present investigation, electron microscopic examination revealed that the uterine septum is formed mainly of smooth muscle fibers similar to those of normal myometrium with numerous blood vessels and little amount of intervening connective tissue. Similarly, Dabirashrafi et al. found that the uterine septum consisted of connective tissue, muscles and blood vessels (25). They reported that the amount of the connective tissue was significantly lower in the septum than in the uterine wall. Using magnetic resonance imaging, Zreik et al. in 1998, reported that uterine septa were frequently composed of myometrial tissue with many muscle fibers (26). Histological evaluation of the resected septal tissue confirmed their finding. Recently, Sparac et al. reported that the intrauterine septa consisted of the

same type of tissue as normal myometrium (14). They also documented the presence of numerous blood vessels inside the septa by transvaginal color Doppler study. They claimed that the muscular tissue within the uterine septum is a potential cause of irregular contractility and consequently increased abortion rates in patients with a septate uterus.

Although Zreik et al. (26) showed an evidence of myometrium in the upper part of the intrauterine septum and that the lower part of the septum was formed of fibrous tissue, the present ultrastructural study revealed the presence of smooth muscle fibers in all parts of the septum (upper, middle and lower). In the upper part of the septum, the smooth muscle fibers were more abundant and more closely opposed, whereas the lower part of the septum demonstrated increased intercellular tissue with abundant collagen fibers.

The differentiation of the endometrial epithelium is a dynamic event that occurs throughout the menstrual cycle and early pregnancy (27). Candiani et al. studied the histological structure of the endometrium covering the septum and reported a slight difference compared with normal endometrium (21). They claimed that this difference could negatively influence the stages of development following implantation particularly the structure of the maternal-fetal relationships which precedes placentation.

Using the scanning electron microscope, this investigation compared the septal endometrium with the endometrium of the lateral uterine wall and revealed that the septal endometrium showed defective preovulatory changes in the form of a reduced number of glandular orifices, irregular nonciliated cells with few or absent microvilli,

incomplete ciliogenesis on ciliated cells and reduced ciliated: nonciliated cell ratio. Fedele et al. examined the endometrial surface morphology in patients with septate uterus and reported similar results (27). These defective changes could be explained by the findings of Sparac et al. who suggested that the endometrial mucosa covering the septum is poorly responsive to estrogens (14).

In conclusion, the results of this ultrastructural study confirm that the uterine septum consists of a very well vascularized fibromuscular tissue. Therefore, the theory of avascular fibrous septum as a cause of pregnancy failure is not acceptable. It is suggested that the few connective tissue elements in the septum may lead to poor decidualization and placentation in the area of implantation with a subsequent poor pregnancy outcome. Moreover, the increased amount of muscle tissue in the uterine septum could result in a higher and uncoordinated contractility causing higher rates of abortion. The observed ultrastructural alterations in the septal endometrium may create an unsuitable medium for the implantation of the blastocyst. The value of hysteroscopic metroplasty as the first line of treatment of septate uterus in women with recurrent abortions is confirmed in this investigation. Therefore, hysteroscopic septum resection is recommended in asymptomatic women with septate uterus as a prophylactic procedure to improve their chances for a successful pregnancy.

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Table I : The demographic data of the studied group (N = 32)

| Variable | Range | Mean \pm S. D. |
|--------------|-----------|------------------|
| Age (years) | 21 - 34 | 27 \pm 3 |
| Gravidity | 5 - 12 | 7 \pm 2 |
| Parity | 2 - 8 | 3 \pm 1 |
| Weight (kgm) | 62 - 95 | 84 \pm 3 |
| Height (cm) | 155 - 178 | 163 \pm 4 |

Table II : The previous obstetric performance of the cases

| Variable | N |
|------------------------------------|----|
| Study group | 32 |
| 1 st trimester abortion | 16 |
| 2 nd trimester abortion | 66 |
| Premature rupture of membranes | 27 |
| Premature labour | 36 |
| Full term delivery | 0 |

N.B. Some women presented by more than one problem

Table III : The obstetric performance of the studied group after hysteroscopic metroplasty

| Variable | N | % |
|------------------------------------|----|------|
| Pregnancies | 29 | 90 |
| 1 st trimester abortion | 1 | 3.6 |
| 2 nd trimester abortion | 2 | 7.1 |
| Premature labour | 2 | 7.1 |
| Full term delivery | 23 | 82.2 |

N.B. The duration of follow up ranged from 6 months up to 3 years

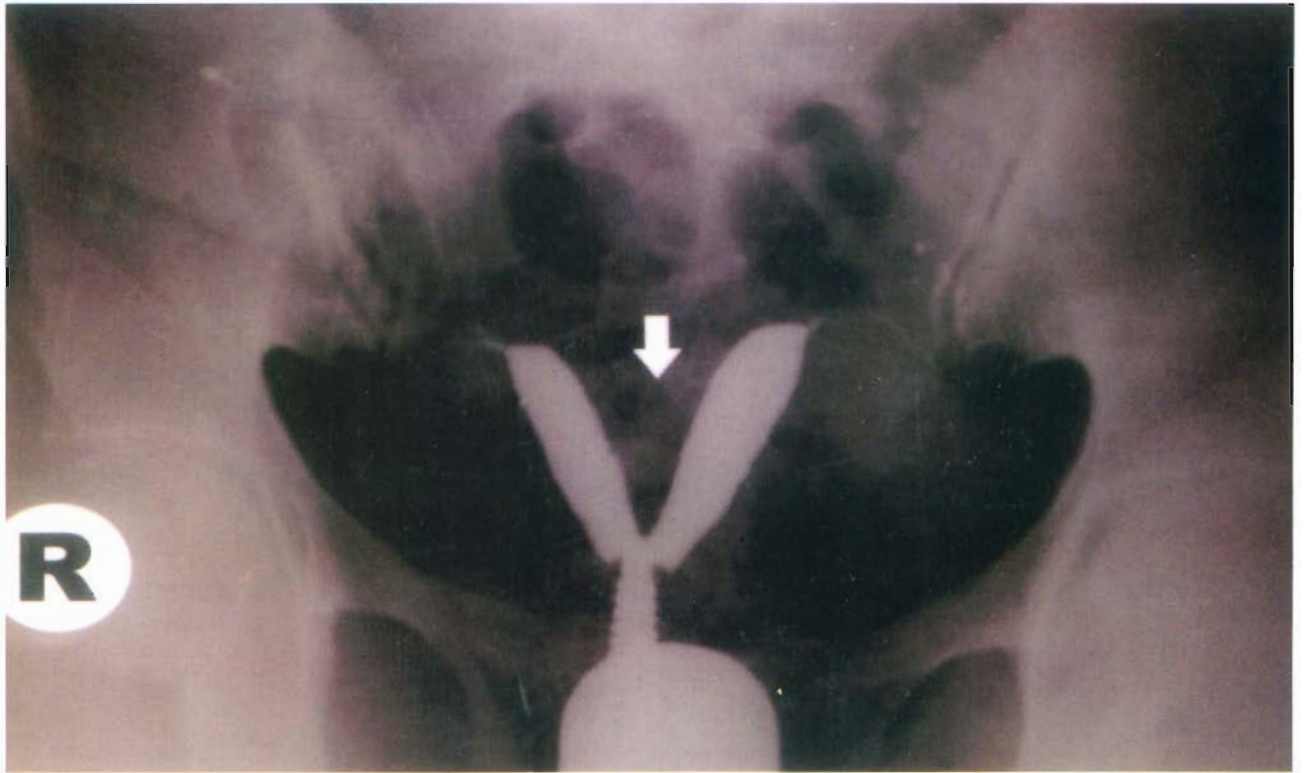


Fig.1. A hysterosalpingogram showing a septate uterus, the uterine septum is marked by the arrow.



Fig.2. A hysteroscopic view of the same case in fig.1 showing an intrauterine septum (S), the uterine cavity is divided into two compartments (*)

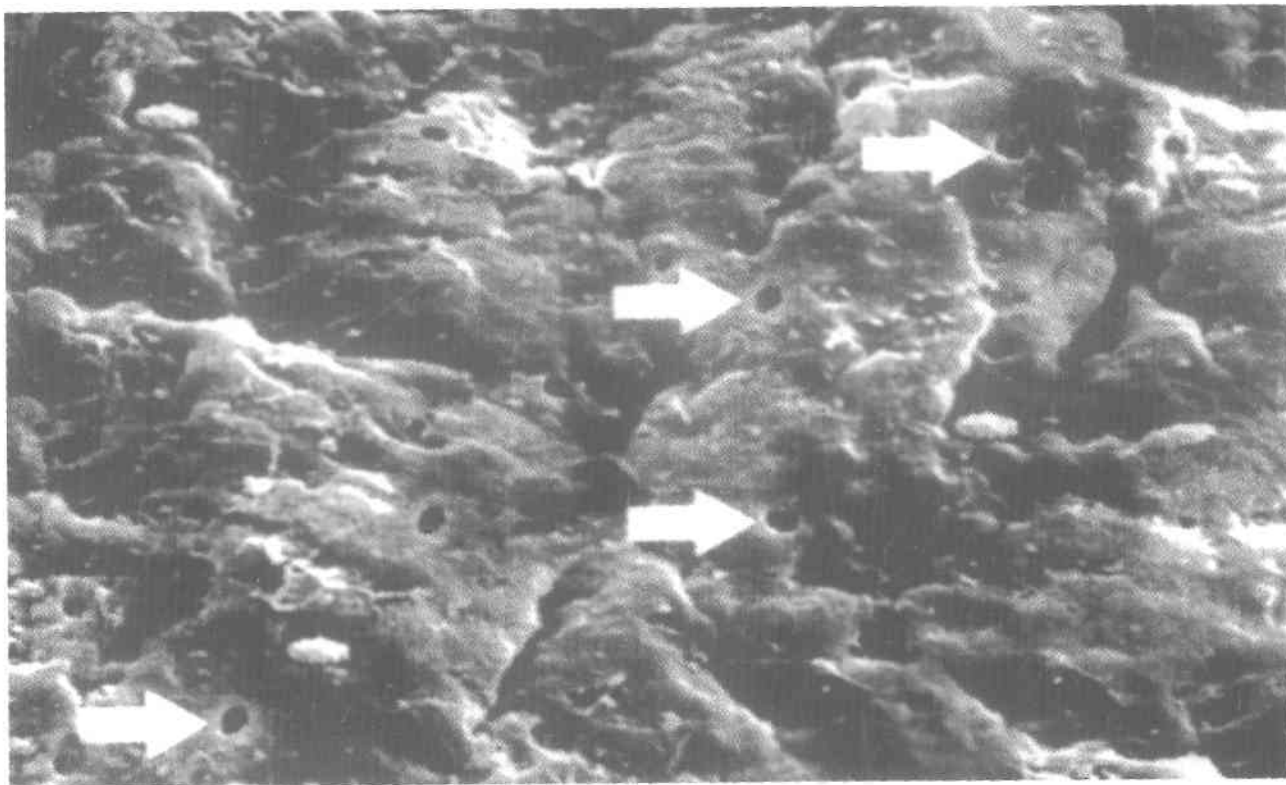


Fig.3. A scanning electron micrograph of endometrium of the lateral uterine wall during the proliferative phase of the menstrual cycle showing numerous uterine gland orifices (arrows) on the surface of the highly folded endometrium. (X110)

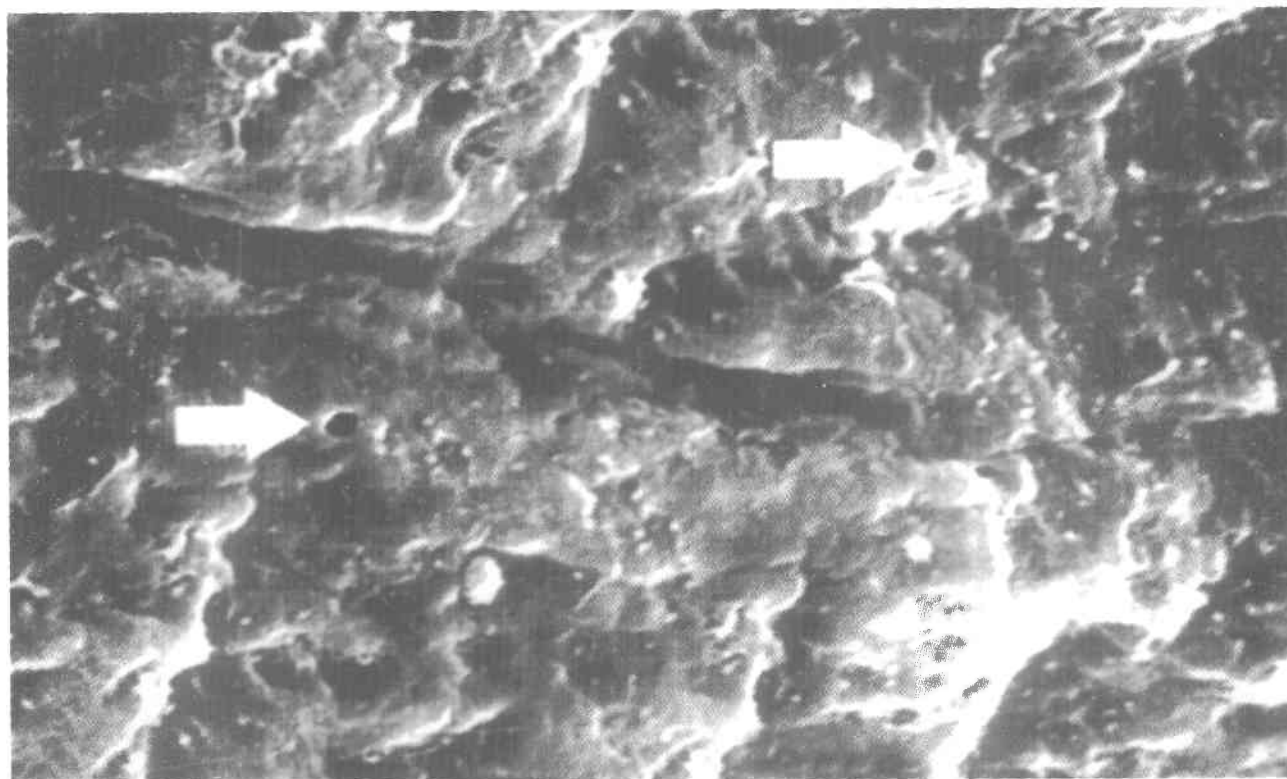


Fig.4. A scanning electron micrograph of septal endometrium of the same case in fig. 3 showing the surface and its plicae with less number of uterine gland orifices (arrows). (X 110).

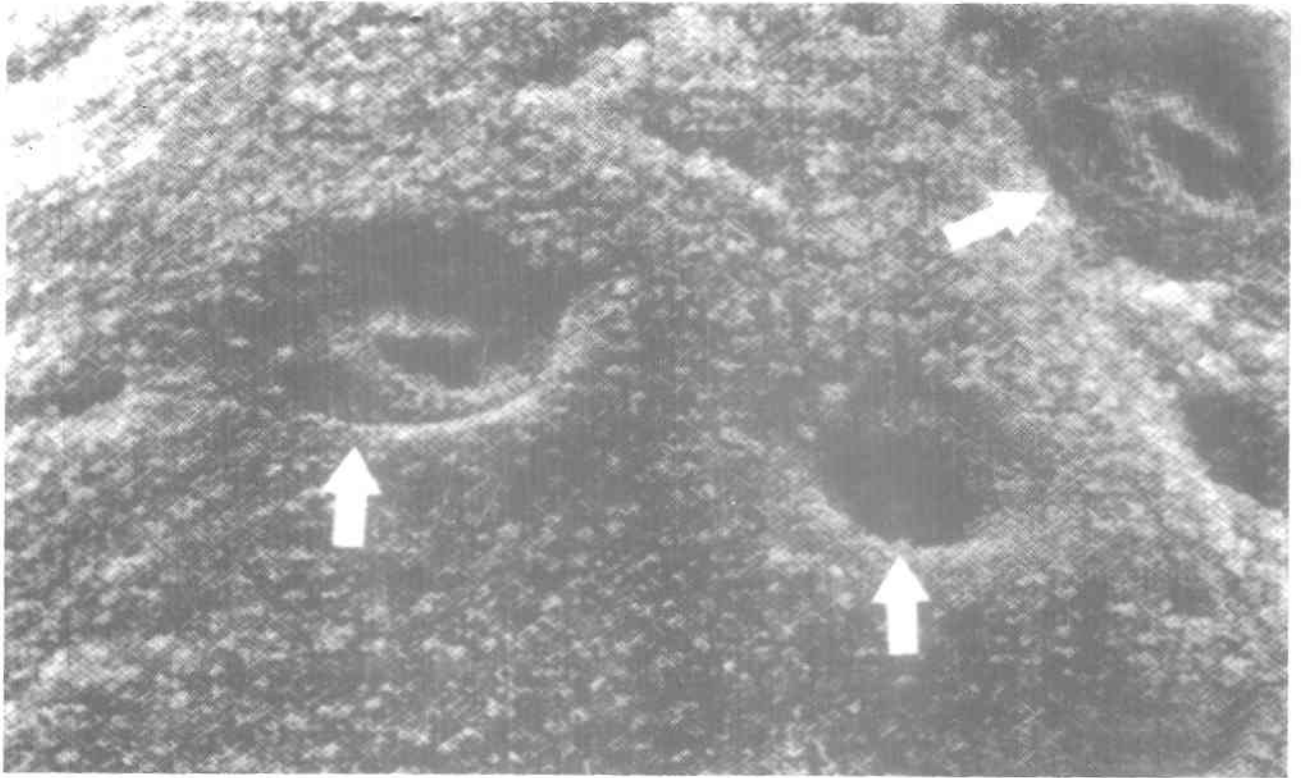


Fig.5. A scanning electron micrograph of normal endometrium during the proliferative phase showing the folded endometrium with numerous uterine gland orifices (arrows). (X 375).

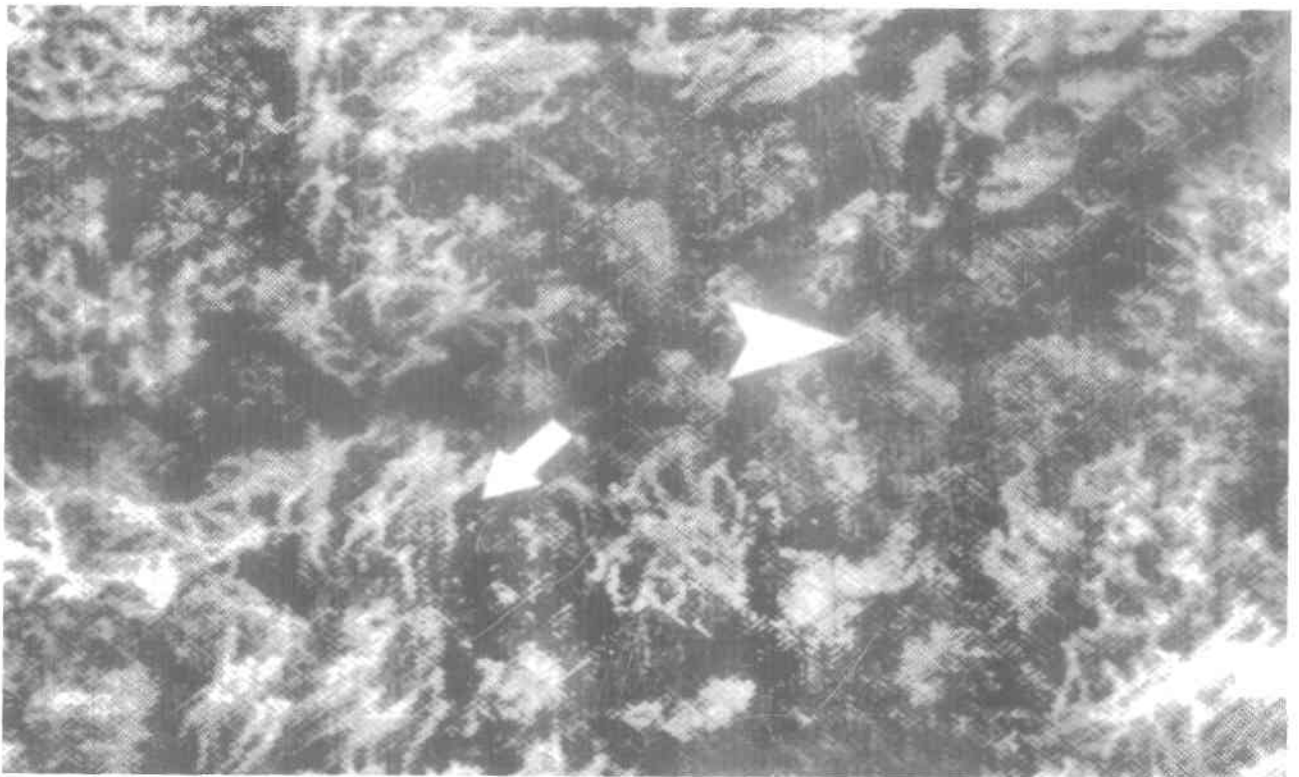


Fig.6. A scanning electron micrograph of the same normal endometrium in fig. 5 showing patches of ciliated cells (arrow) interspersed with nonciliated secretory cells (arrowhead). Note the dense ciliation and the convex apices of the secretory cells covered with regular microvilli. (X3, 750)

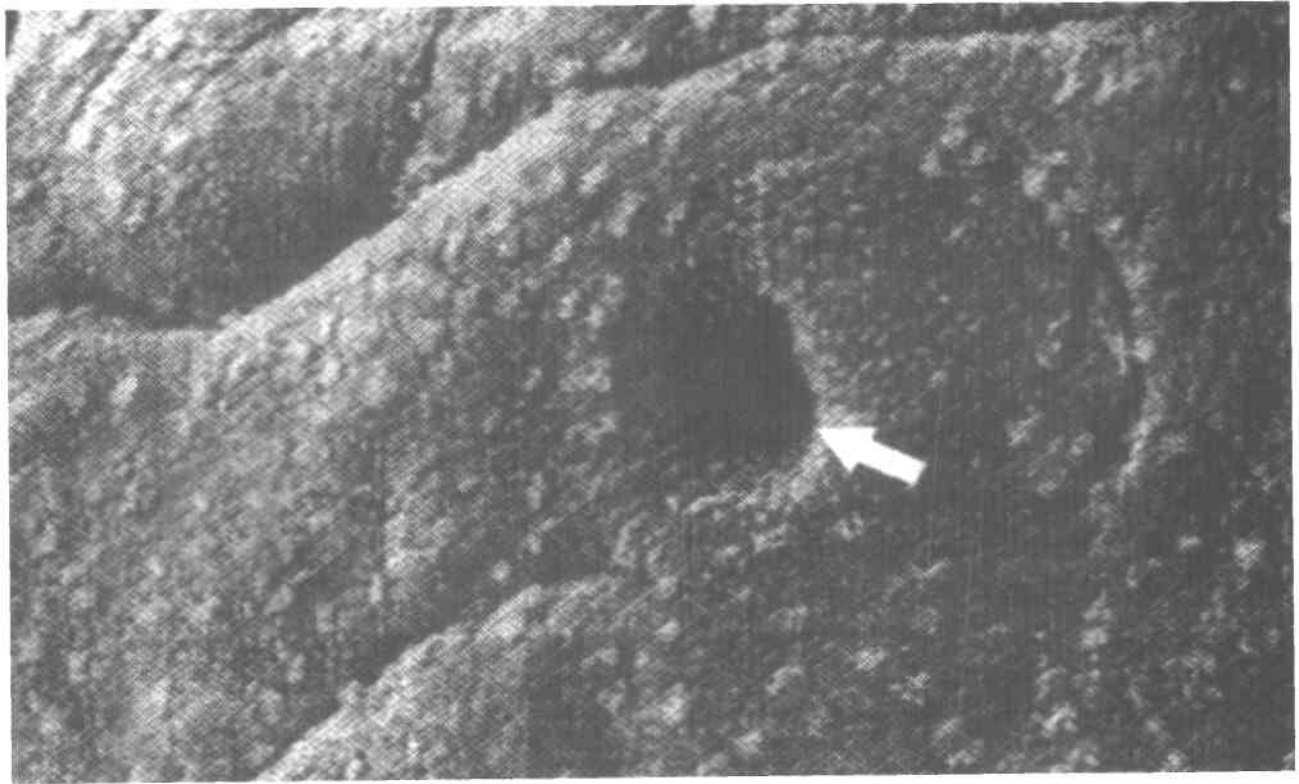


Fig.7. A scanning electron micrograph of the septal endometrium of the same case in fig. 5 showing fewer numbers of glandular orifices (arrow) (X 375).

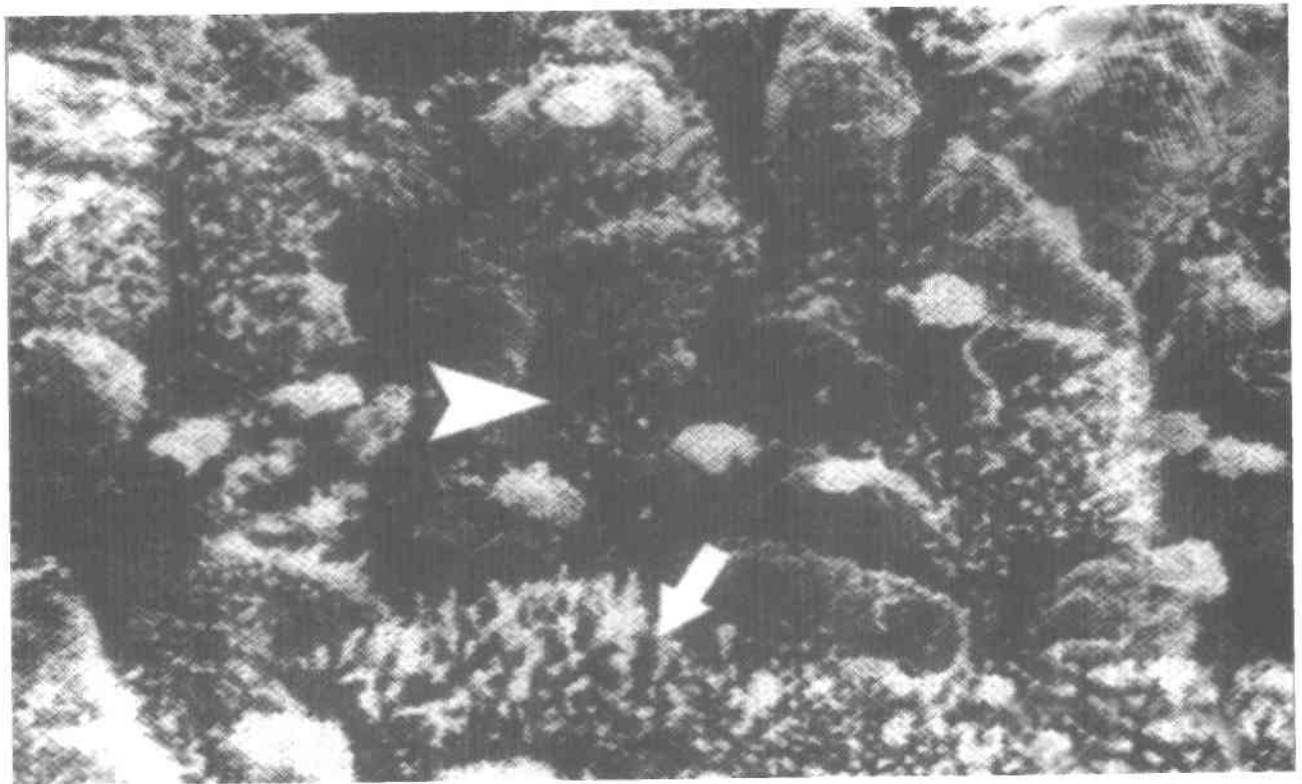


Fig. 8. A scanning electron micrograph of the uterine septal endometrium of the same septum in fig. 7 showing fewer numbers of ciliated cells with few short cilia (arrow). The nonciliated cells appear irregular with few irregular microvilli (arrowhead). (X 3, 750)

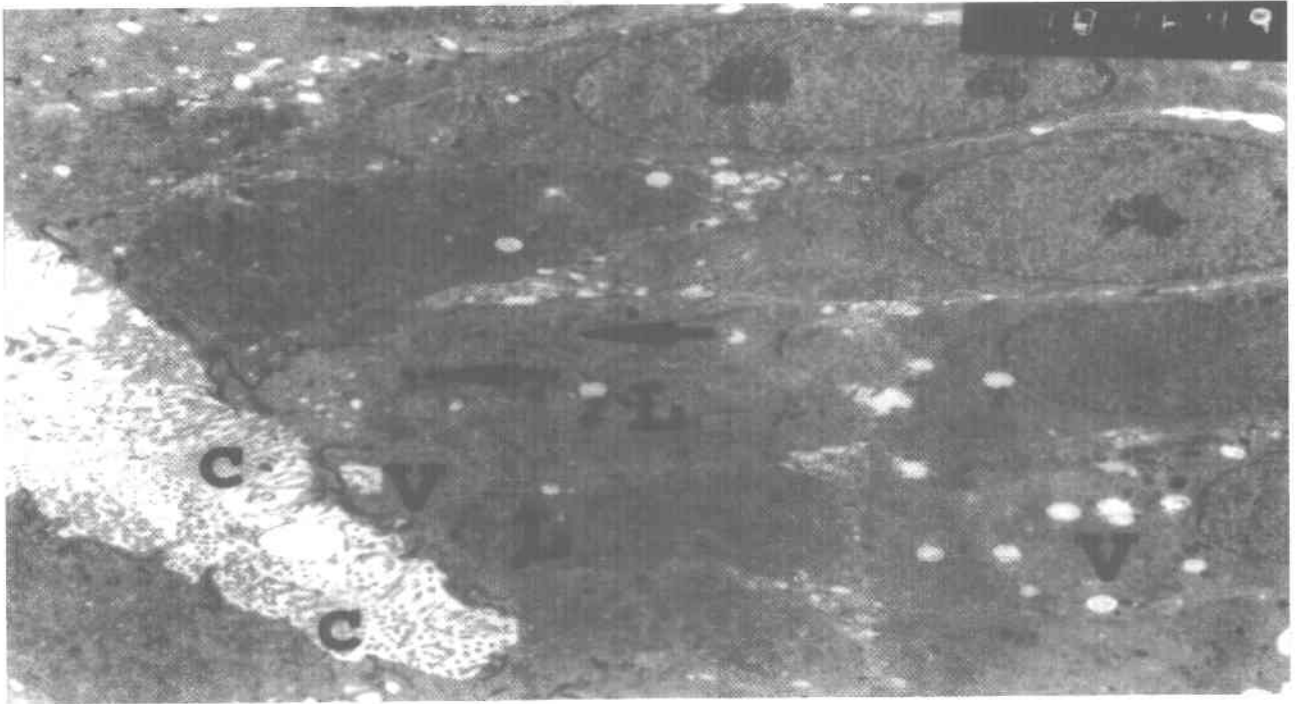


Fig.9. A transmission electron micrograph of endometrium of the lateral uterine wall during the proliferative phase of the menstrual cycle showing a group of columnar ciliated cells. the cilia (C) are regular and numerous. The apical cytoplasm of the ciliated cells contains numerous mitochondria (arrows), many electron-dense lysosomes (L) and many cytoplasmic vacuoles (V). (X 4, 500)

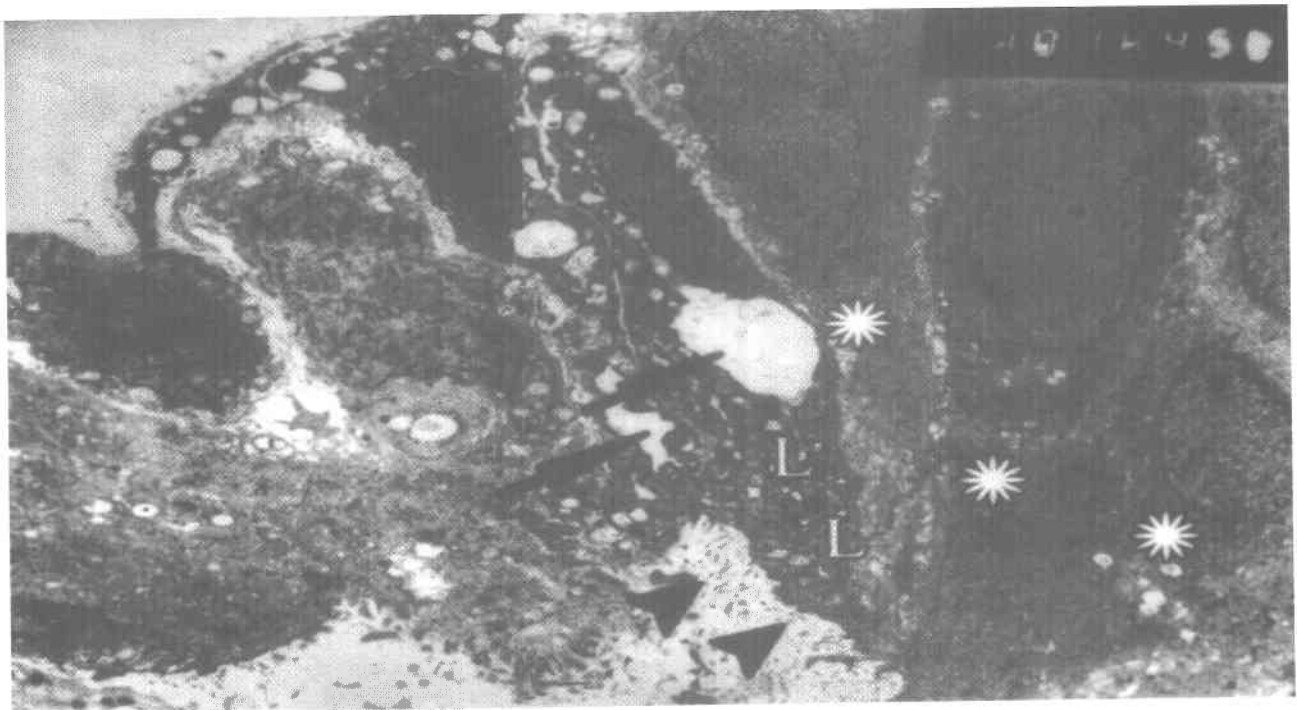


Fig. 10. A transmission electron micrograph of endometrium of the lateral uterine wall during the proliferative phase showing small groups of ciliated cells (stars) and nonciliated secretory cells. The secretory cells contain widely dilated profiles of endoplasmic reticulum distended with electron-lucent or moderately electron-dense material (arrows) and electron-dense lysosomes (L) of variable sizes. The luminal surface of the secretory cells has fairly numerous regular microvilli (arrowheads). (X 4,500).

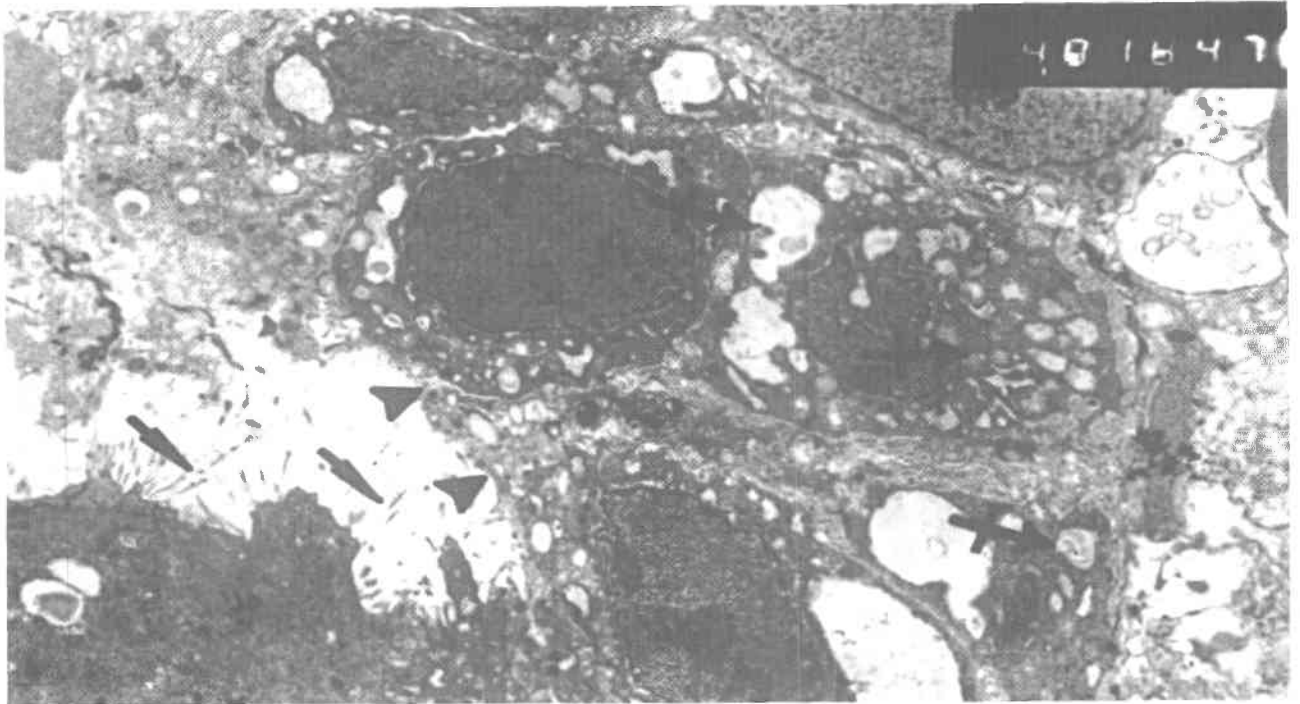


Fig.11. A transmission electron micrograph of septal endometrium of the same uterus showing few ciliated cells and a group of many secretory cells. The luminal border of the ciliated cells exhibits few short cilia (arrows). The cytoplasm of the secretory cells contains widely dilated profiles of endoplasmic reticulum (crossed arrows) whereas their luminal borders lack microvillia (arrowheads). (X 4,500).

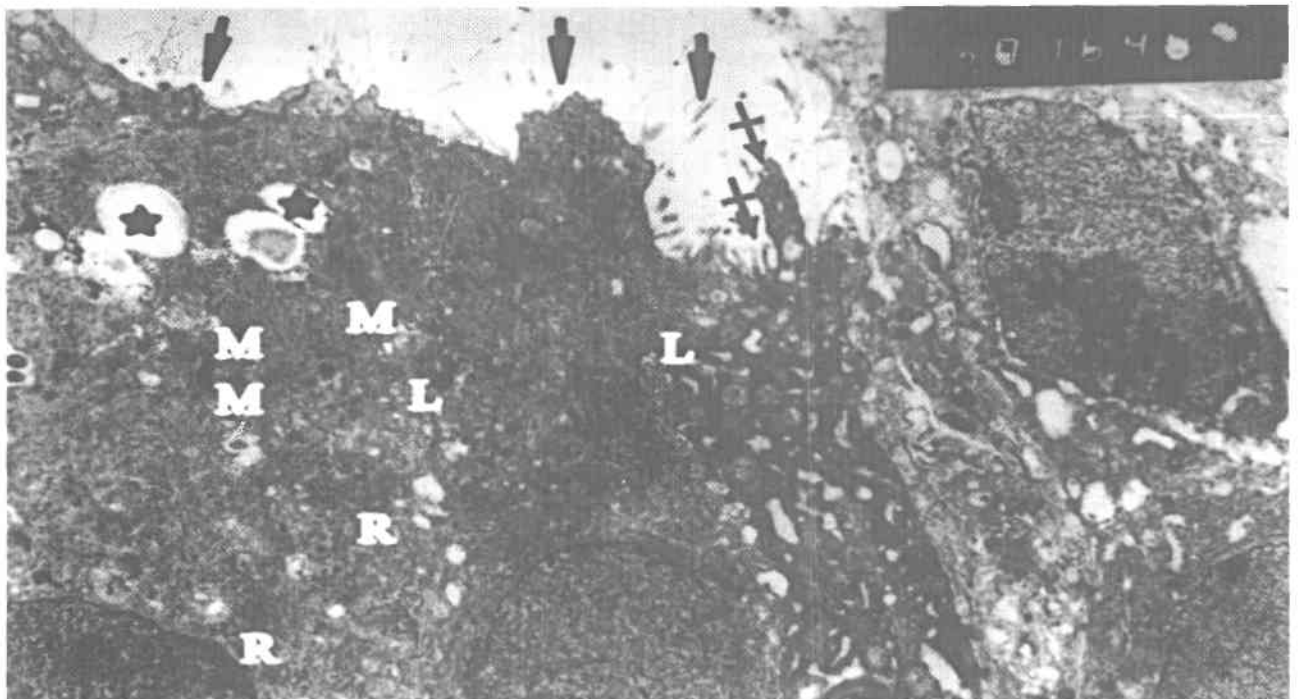


Fig. 12. A higher magnification of the previous figure showing the few short cilia (arrows) of ciliated cells and the few microvilli (crossed arrows) on the surface of the secretory cells. The cytoplasm of the ciliated cells contain numerous apical mitochondria (M), ribosomes (R), lysosomes (L) and vacuoles (stars) of variable sizes. The cytoplasm of the secretory cells is full of widely dilated profiles of endoplasmic reticulum distended with electron-lucent or moderately electron-dense material. (X 5,750).

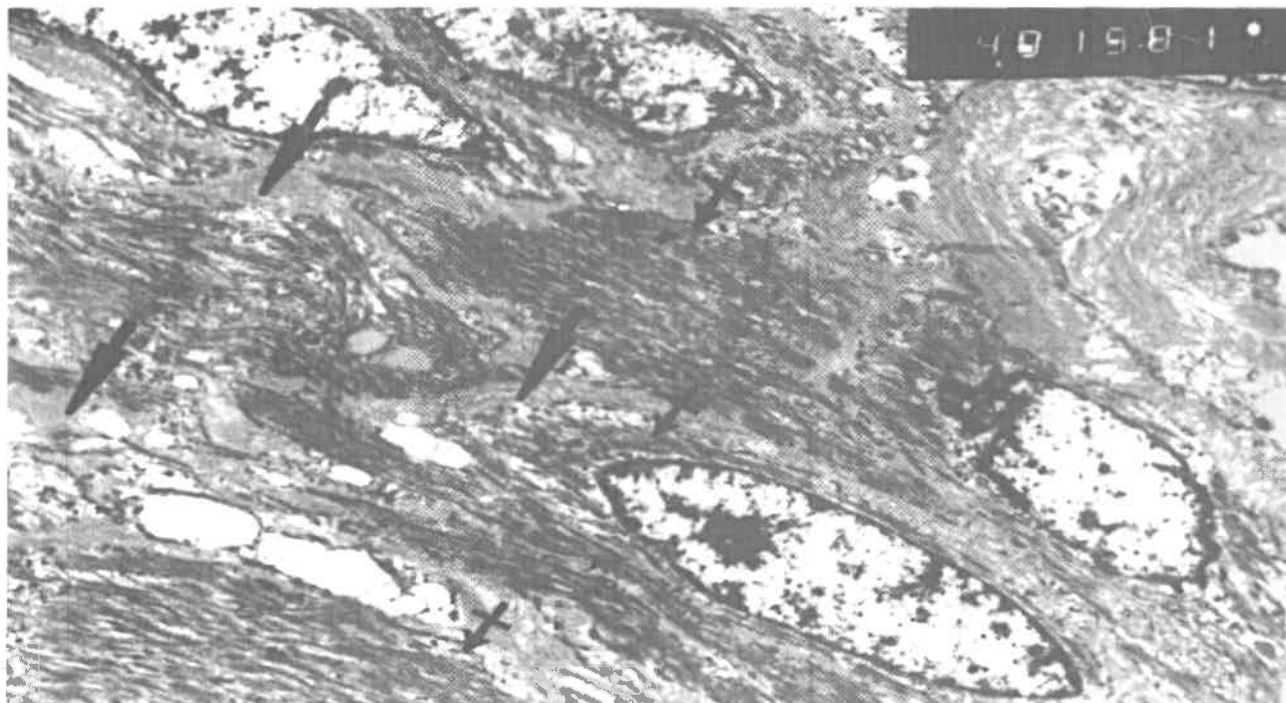


Fig. 13. A transmission electron micrograph of the upper part of the uterine septum showing longitudinally cut smooth muscle cells (fibers) with elongated vesicular nuclei. The muscle cells are closely opposed with little intercellular material containing small collagen bundles (arrows). The sarcoplasm shows prominent myofilaments (crossed arrows) running longitudinally. (X 4,500).

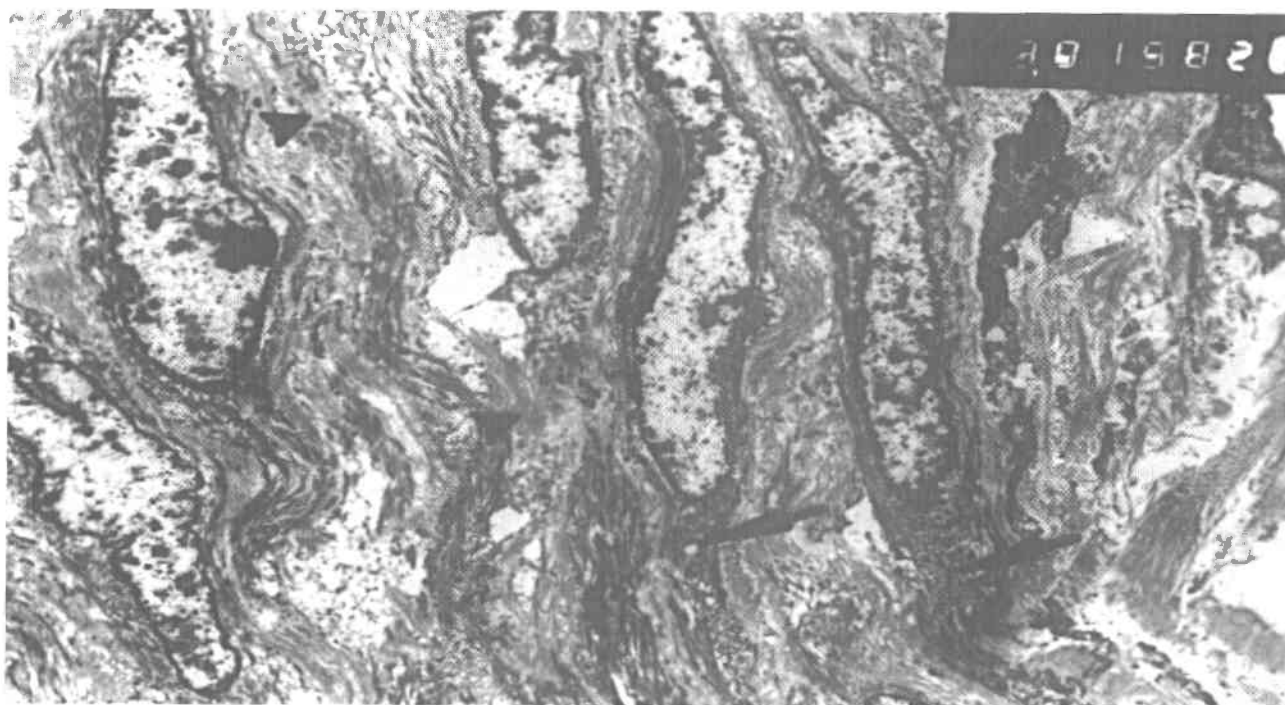


Fig. 14. A transmission electron micrograph of the middle part of the uterine septum during the proliferative phase showing longitudinally cut smooth muscle fibers with elongated vesicular nuclei and longitudinally oriented myofibrils. The cell organelles tend to aggregate at the nuclear poles (arrows). The muscle cells are separated by more connective tissue containing collagen bundles (arrowheads). (X 4,500).

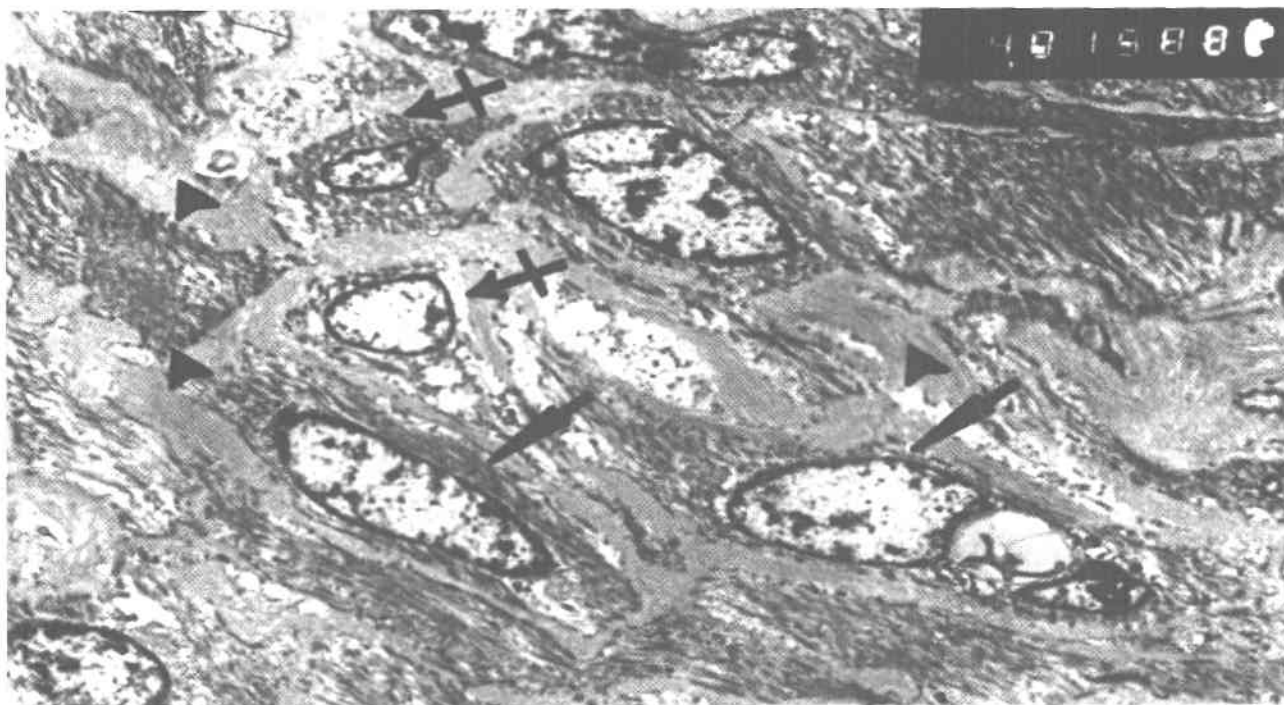


Fig.15. A transmission electron micrograph of the lower part of the septum of the same uterus. The smooth muscle fibers are cut both longitudinally (arrows) and transversely (crossed arrows). They have vesicular nuclei and prominent myofilaments. Notice the increased intercellular material with abundant collagen bundles (arrowheads). (X 4,500).

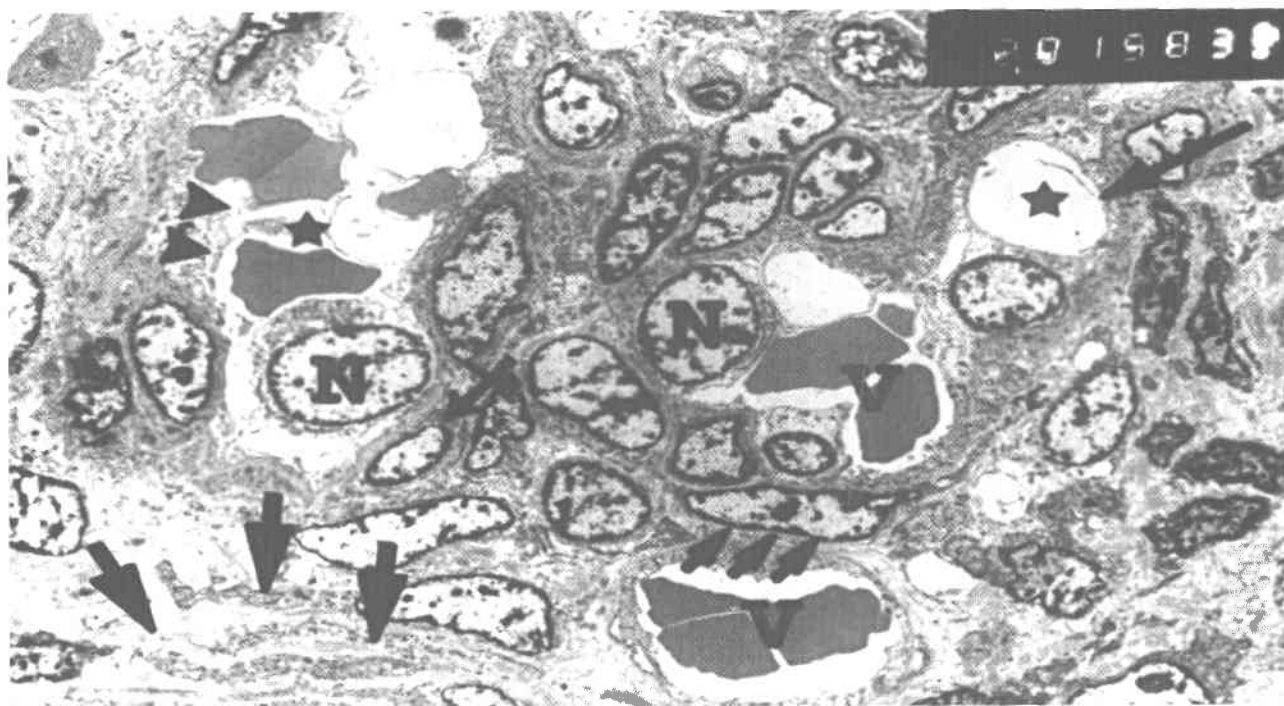


Fig. 16. A transmission electron micrograph of a highly vascularized area of the uterine septum. Blood capillaries (stars) and venules (V) are seen with erythrocytes in their lumina. The capillary endothelium may be continuous (long arrow) or fenestrated (arrowheads). The venules are partly surrounded with muscle fibers (short arrows). Notice the prominent nuclei of endothelial cells (N), the nuclei of associated pericytes (crossed arrows) and septal smooth muscle cells (thick arrows). (X 4,500).