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Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility

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Women suffering from infertility in association with mostly mild endometriosis were subjected to vaginal sonography of uterine peristalsis during the menstrual period, the early, mid- and late follicular phases, and the mid-luteal phase of the menstrual cycle. The data obtained were compared with those of healthy controls. Women with endometriosis displayed a marked uterine hyperperistalsis that differed significantly from the peristalsis of the controls during the early and mid-follicular and mid-luteal phases. During the late follicular phase of the cycle, uterine peristalsis in women with endometriosis became dysperistaltic, arrhythmic and convulsive in character, while in controls peristalsis continued to show long and regular cervico–fundal contractions. Hysterosalpingoscintigraphy during the early, mid- and late follicular phases revealed that hyperperistalsis in the early and mid-follicular phases of patients with endometriosis resulted in a dramatic increase in the transport of inert particles from the vaginal depot, through the uterus into the tubes and also into the peritoneal cavity. During the late follicular phase of the cycle, the dysperistalsis observed in women with endometriosis resulted in a dramatic reduction of uterine transport capacity in comparison with the healthy controls. We consider uterine hyperperistalsis to be the mechanical cause of endometriosis rather than retrograde menstruation. Dysperistalsis in the late follicular phase of patients with endometriosis may compromise rapid sperm transport. Uterine hyperperistalsis and dysperistalsis are considered to be responsible for both reduced fertility and the development of endometriosis.

Key words: dysperistalsis/endometriosis/hyperperistalsis/infertility/sperm transport

Introduction

Recently it was demonstrated, by utilizing the methods of vaginal sonography of uterine peristalsis (VSUP) and hysterosalpingoscintigraphy (HSSG), that rapid sperm transport through the female genital tract provided by cervico–fundal peristaltic contractions of the uterus, which increase in frequency and intensity as the proliferative phase progresses, is directed preferentially into the tube ipsilateral to the dominant follicle; it is therefore considered to be under the control of the dominant follicle (Kunz *et al.*, 1996). Here we report an extension of our studies and provide evidence that the mechanism of rapid sperm transport is fundamentally disturbed in patients with endometriosis and infertility. These patients exhibit, as demonstrated by VSUP and HSSG, a considerable degree of uterine hyper- and dysperistalsis. It is concluded that a dysfunction of the mechanism of rapid sperm transport contributes significantly to the development of endometriosis and infertility in these patients. We assume that uterine hyperperistalsis as a dysfunction of the physiological mechanism of rapid sperm transport, rather than retrograde menstruation, constitutes the mechanical cause of endometriosis.

Materials and methods

Patients

A total of 205 women aged 21–46 years (mean 30) entered this study following informed consent. Of these, 111 women aged 21–38 years (mean age 29) had a history of infertility of 1–7 years (mean 4) and were suffering from endometriosis as demonstrated by laparoscopy. Most of these patients were suffering from minimal or mild endometriosis (n = 82), and the rest from moderate or severe endometriosis (n = 29), according to the revised classification of the American Society of Reproductive Medicine (formerly American Fertility Society, AFS). In all patients, tubal patency was demonstrated by laparoscopy

Most of the patients had regular cycles Some displayed prolonged proliferative and short luteal phases While all these patients were subjected to VSUP, a smaller proportion of the patients (n = 51) were subjected to HSSG only.

A group of 94 women aged 22–46 years (mean 30) served as controls. All had regular cycles, a history of fertility or their partners were suffering from andrological sterility. In the group of women undergoing vaginal sonography for uterine peristalsis (n = 66), none had endometriosis, 18 were of proven fertility and 48 suffered from secondary tubal or andrological sterility. Tubal sterility and endometriosis were excluded by laparoscopy in all women undergoing HSSG (n = 28).

Vaginal sonography of uterine peristalsis (VSUP)

VSUP was performed with a 7.5 MHz probe (Sonoline SI-45; Siemens, Erlangen, Germany). The probe was placed in a position to yield a sagittal section of the whole uterus and was kept in a fixed position for 5 min. The whole scan was video taped for the quantitative assessment of uterine peristalsis. To obtain a precise estimate of the frequency of the contraction waves, the tape was replayed at five

times the regular speed This also facilitated the determination of the direction of the waves (cervico–fundal versus fundo–cervical peristalsis)

Hysterosalpingoscintigraphy (HSSG)

HSSG was performed according to the method described by Iturralde and Venter (1981) and Becker *et al.* (1988) and specified by Kunz *et al.* (1996). Albumin macrospheres (Solco MAA; Nuclear GmbH, Grenzach-Wyhlen, Germany), with a 95% mean diameter of 5–40 μm, were labelled with technetium-99m and suspended in normal saline for 5 min prior to application. A 0.5 ml aliquot of the suspension containing ~2×10^6 labelled albumin particles with a radioactivity of ~25 MBq with <0 1% free technetium was placed by a syringe into the posterior vaginal fornix with the patient in the supine position, which was not changed during the whole procedure

Serial anterior–posterior scintigrams were performed with a gamma camera (Orbiter; Siemens) over 32 min, starting 1 min after application of the suspension. During the first 18 min the radioactivity was measured every 1 min, and thereafter every 2 min

For the assessment of the ascension of the labelled macrospheres, the genital tract was subdivided into three compartments: the upper vagina, the place of application, was compartment 1, and the uterine cavity and the isthmical part of the tubes were compartments 2 and 3 respectively. In all patients the localization of the dominant follicle was, whenever possible, documented. Thus, in the assessment of the ascension into compartment 3, transport into the right or left or into the tube ipsi- or contralateral to the dominant follicle was distinguished. The ampullary part of the tubes and the peritoneal cavity were designated compartment 4 (Kunz *et al.*, 1996). Because it was, in general, difficult to distinguish clearly between compartments 3 and 4, data from these two compartments were combined in the quantitative assessment of transport beyond the confines of the uterine cavity.

The camera used provided colour prints with a spectrum of colours ranging from black to yellow and red to blue, thus demonstrating roughly the relative distribution of radioactivity, with black indicating the highest and blue the lowest intensity measured For a quantitative assessment of the ascension of the labelled albumin macrospheres within the genital tract, the scans of 1, 16 and 32 min following application of the particles were selected, and regions of interest corresponding to the chosen compartments determined independently by a radiologist and a gynaecologist. The counts were measured within each compartment and expressed as percentages of the total counts

VSUP was performed during the menstrual period, the early, mid- and late follicular phases, and the mid-luteal phase of the cycle, whereas HSSG was performed during the early, mid- and late follicular phases only These phases were related to the ovarian functional status by determining the diameter of the dominant follicle by vaginal sonography and the measurement of serum oestradiol and progesterone concentrations by a commercially available radioimmunoassay kit (Progesterone and Oestradiol Maia; Serono Diagnostika GmbH, Freiburg Germany). In patients with prolonged follicular phases caused by a delayed onset of follicular maturation, as determined by ultrasound, assignment to the respective stage of the follicular phase was based on the results of vaginal sonography with respect to the absence or presence of a dominant follicle and its diameter, as well as on the results of the steroid measurements in serum Thus, patients with an abnormal length of their proliferative phase could also enter the study Following VSUP and HSSG, the cycles were monitored further by ultrasound and/or progesterone concentration measurements Thus it was ensured that all studies were performed in ovulatory cycles Patients were advised not to conceive during an HSSG cycle. No conception occurred in such a cycle

Statistical analysis

The statistical analysis was performed using Student's *t*-test.

Results

VSUP

The results obtained after VSUP are demonstrated in Figures 1 and 2. As shown in Figure 1, in healthy women the frequency of contractions increased from 1.2 contractions/min in the early follicular phase to >1.5 contractions/min during the mid-follicular phase and up to 2.5 contractions/min during the late follicular phase. There was no statistical difference in the frequencies of contraction between the later stages of menstruation and the early follicular phase. During the whole follicular phase there was a steady decrease in the proportion of fundo–cervical contractions, from nearly 50% in the later stage of menstruation down to 1% during the late follicular phase. During the mid-luteal phase the frequency of contractions decreased again and was similar to that of the mid-follicular phase, with 90% of the contractions being cervico–fundal in direction.

Patients with endometriosis displayed a dramatic increase in uterine peristaltic contractions (Figure 1). With nearly a doubling of the frequencies during the early, mid- and late follicular phases, as well as the mid-luteal phase, the values differed significantly from the corresponding ones in healthy women. Although the frequencies of contraction during the menstrual period and the late follicular phase were apparently also increased relative to the respective controls, these differences were not significant ($P = 0.06$; late follicular phase). With the progression of the cycle, the fundo–cervical contractions decreased as in the controls.

During the late follicular phase the character of the peristaltic waves in patients with endometriosis differed fundamentally from that of the controls. While in the controls the contraction waves were long and regular, they had an irregular appearance in patients with endometriosis. Some of the contractions originated in the middle portion of the uterus and spread simultaneously to the fundus and the cervix. Other contractions started simultaneously at different sites, creating a convulsive appearance of the uterine activity, while some vanished before they had reached the fundal part of the uterus. Thus the contractile activity of the uterus displayed the characteristics of dysperistalsis and arhythmia.

Figure 2 shows the distribution of the individual frequencies of contractions observed during the mid-follicular and luteal phases of 36 healthy women in comparison with the corresponding distribution of frequencies of contractions in 31 women, of whom 21 were suffering from mild and 10 from severe endometriosis (grades I and IV respectively, according to the classification of the American Society of Reproductive Medicine) In each of these cycle phases the individual frequencies of uterine peristalsis were normalized to the mean frequency of the healthy women as 100%. The graph obtained demonstrated the close association of the occurrence of endometriosis with hyperperistalsis. There was no association between the degree of hyperperistalsis and the grades of endometriosis according to the revised AFS classification.

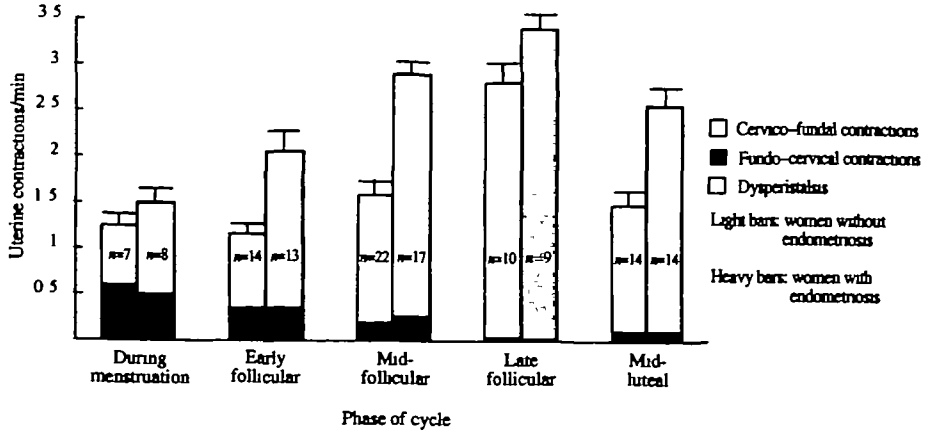

Figure 1. A graphical demonstration of the frequency of the subendometrial uterine peristaltic waves during menstruation, the early, mid- and late follicular and mid-luteal phases of the cycle as determined by vaginal ultrasonography (contractions/min ± SEM) in women with and without endometriosis. The graph also shows the relative distribution of fundo–cervical contractions versus cervico–fundal contractions during these different phases of the cycle. During the early follicular, mid-follicular and mid-luteal phases the peristaltic activity differed significantly between the two groups of patients ($P < 0.05$). During the late follicular phase the increased peristaltic activity in patients with endometriosis in comparison with the healthy controls ($P = 0.06$) has attained the character of dysperistalsis.

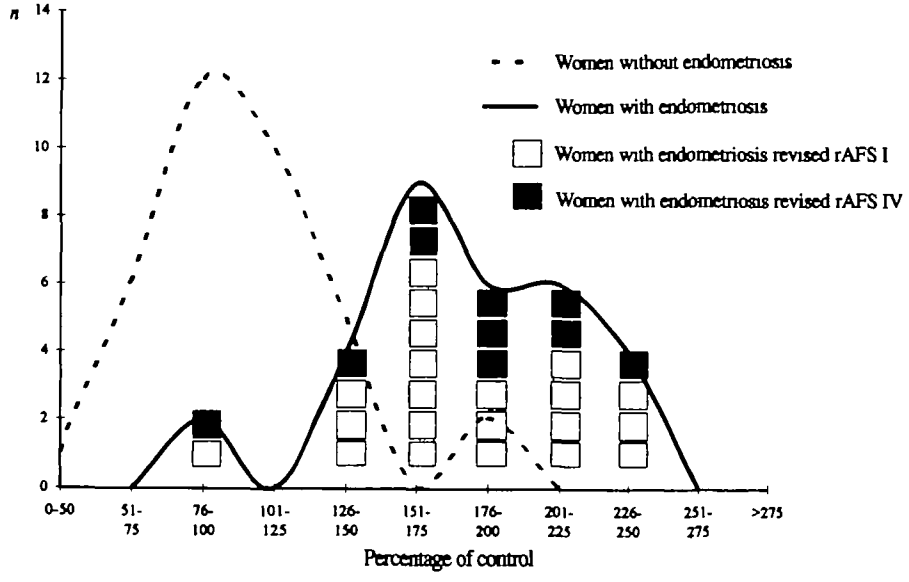

Figure 2. The distribution pattern of uterine peristalsis with respect to the absence (dashed line) ($n = 36$) or presence (solid line) ($n = 31$) of endometriosis. Data from the mid-follicular and mid-luteal phases of the cycle were used. The peristaltic frequency was normalized to the mean frequency in women without endometriosis as 100%. In women with endometriosis, the grade of the disease according to the revised American Fertility Society classification (American Society for Reproductive Medicine) is also indicated.

HSSG

The results of HSSG are depicted in Figures 3–6. Figure 3 is a representative picture of HSSG images obtained in three different women each with grade I revised AFS endometriosis respectively during the early, mid- and late proliferative phases of the cycle, at 1, 16 and 32 min following application of the labelled macrospheres. Already in the early follicular phase a rapid ascension of the macrospheres up to compartment 3 within the first 16 min after application was observed, which in healthy women occurred not before the late proliferative phase of the cycle (Kunz *et al.*, 1996). The example of the mid-follicular phase showed the massive ascension of particles from the vaginal depot over the left tube into the pouch of Douglas. The dominant follicle developed on the contralateral side. In the example of the late follicular phase it was demonstrated that much of the radioactivity remained at the site of application and only a little activity was transported beyond the confines of the uterus.

Figures 4–6 demonstrate a summary of these findings following a quantitative assessment of the distribution of radioactivity in women with endometriosis in comparison with healthy controls. In normal women the highest proportion of macrospheres remained at the site of application

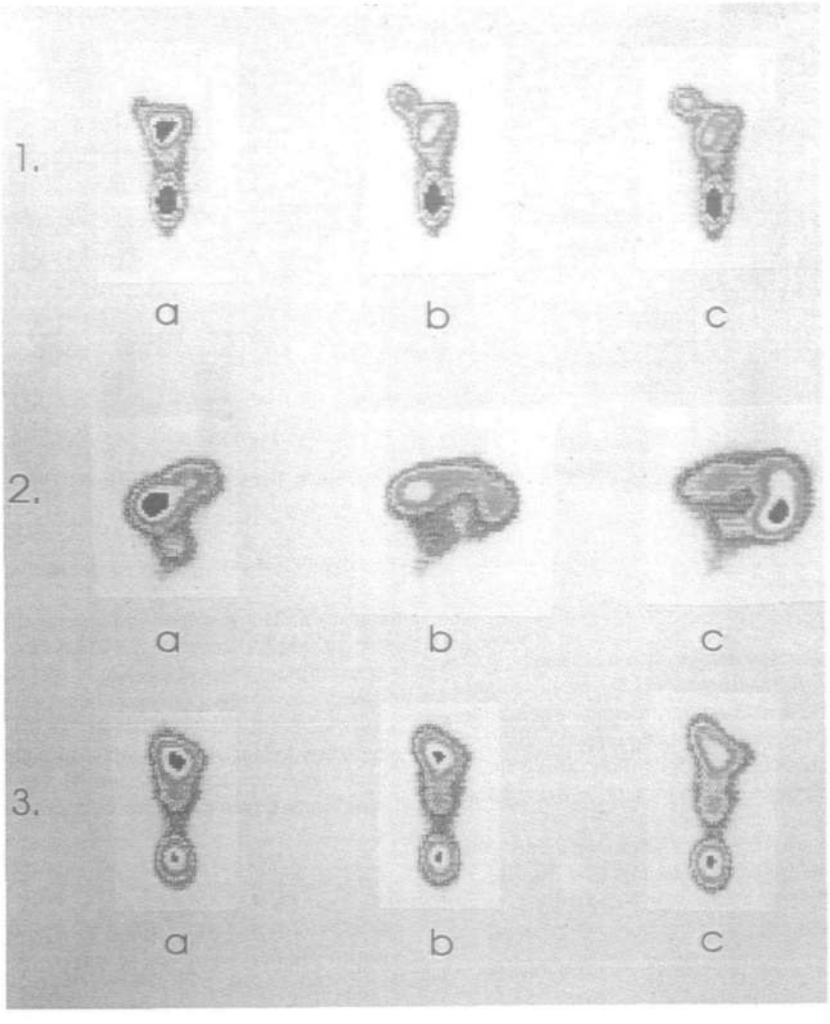

Figure 3. Representative colour prints obtained by hysterosalpingoscintigraphy in three different patients no. 1, early follicular phase; no. 2, mid-follicular phase; no. 3, late follicular phase. In each patient, scintigrams were performed at 1–2 min intervals In this figure only the scintigrams following 1 min (**a**), 16 min (**b**) and 32 min (**c**) after the vaginal application of the labelled macrospheres are depicted. In the patient of the mid-follicular phase, the dominant follicle was situated in the right ovary, while the macrospheres entered the left tube In the patient of the late follicular phase, the dominant follicle was situated in the left ovary, while the macrospheres tended to enter the right tube.

during the early follicular phase, and these were increasingly aspirated from the vaginal depot and transported through the uterine cavity preferentially into the tube ipsilateral to the dominant follicle (Figures 4–6, upper panels). This pattern has been described in detail elsewhere (Kunz *et al.*, 1996).

In women with endometriosis, already at 1 min after application of the macrospheres, there was a significant aspiration of the particles from the vaginal depot into the uterine cavity and further transport into both tubes. The amount of radioactivity that entered the tubes in patients with endometriosis was significantly larger ($P < 0.01$) in comparison with normal women at 1, 16 and 32 min after vaginal application.

In the mid-follicular phase of the cycle (Figure 5) there was a decrease of radioactivity in compartment 2 at 1, 16 and 32 min after application in women with endometriosis, which was significant ($P < 0.01$) in the 16 and 32 min scintigrams in comparison with the controls, and corresponded to an increase in radioactivity in the tube contralateral to the dominant follicle The amount of radioactivity in the tube contralateral to the dominant follicle was significantly higher ($P < 0.01$) over the whole period of measurement in comparison with the controls.

In the late follicular phase of the cycle (Figure 6) a peculiar distribution pattern of radioactivity was observed in patients with endometriosis. The pattern was similar to that found in the early follicular phase of normal patients. Most of the activity remained at the site of application, little was transported into the tubes and there was no preference for either tube. In healthy women, there was an up to three times larger amount of radioactivity in the tube ipsilateral to the dominant follicle in comparison with women with endometriosis ($P < 0.05$).

Tables I and II show the endocrine characteristics as well as the follicular diameters in the subjects studied. No

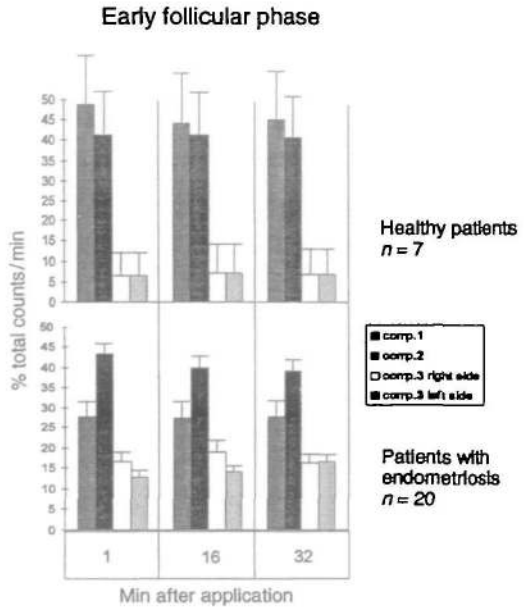

Figure 4. The distribution of the percentage of total counts, representing the labelled albumin macrospheres, within the female genital tract (compartments 1, 2 and 3 being the upper vagina, the uterine cavity and the isthmical part of the tubes respectively) following 1, 16 and 32 min after vaginal application during the early follicular phase. With respect to compartment 3, the right and left tubes were differentiated. The amount of radioactivity transported into the tubes was significantly higher in patients with endometriosis in comparison with healthy controls ($P < 0.01$).

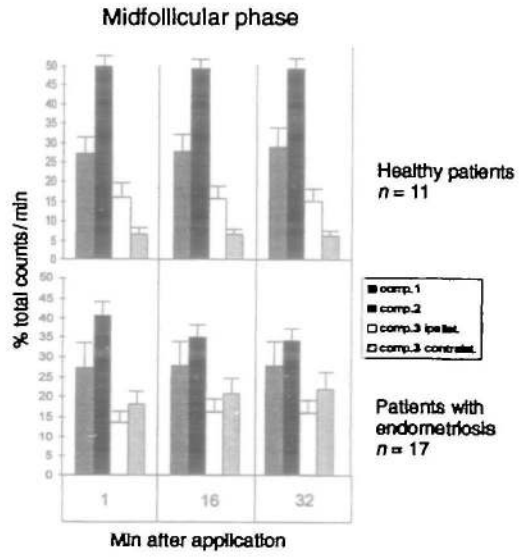

Figure 5. The respective distribution patterns of radioactivity, as in Figure 4, obtained during the mid-follicular phase of the cycle. While in patients without endometriosis the labelled macrospheres preferentially entered the tube ipsilateral to the dominant follicle, in patients with endometriosis the macrospheres preferentially entered the tube contralateral to the dominant follicle. The difference in ascension into the contralateral tube between the two groups of patients was significant ($P < 0.01$).

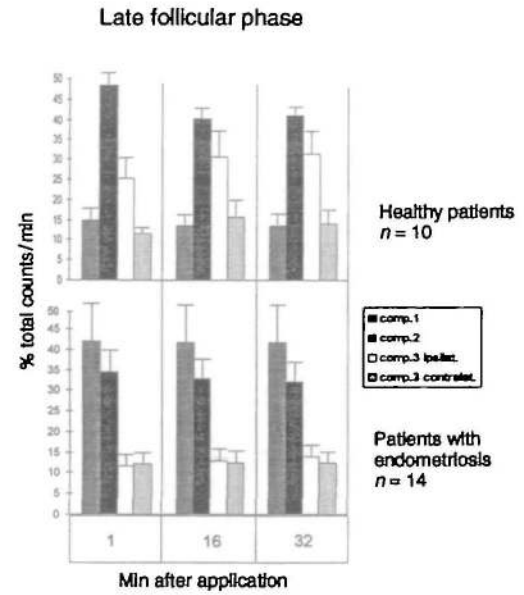

Figure 6. The distribution patterns of macrospheres, as in Figure 4, during late follicular phase. While the macrospheres preferentially entered the dominant ipsilateral tube in healthy women, the dysperistalsis observed in patients with endometriosis during this stage of the follicular phase resulted in a breakdown of transport capacity, leading to a distribution pattern of the macrospheres that resembled the pattern for normal women during the early proliferative phase (Figure 4; upper panel).

differences between the two populations with respect to the endocrine and follicular parameters were noted.

Discussion

Using both VSUP and HSSG, it was shown that, in healthy women with normal cycles and no evidence for endometriosis, rapid and doubtless sustained sperm transport through the female genital tract from the external os of the cervix into the tubes is provided by cervico–fundal uterine peristaltic waves that increase in frequency and presumably intensity as the follicular phase progresses (Birnholz, 1984; Oike *et al.*, 1988; Abramovicz and Archer, 1990; De Vries *et al.*, 1990; Lyons *et al.*, 1991; Kunz *et al.*, 1996). While spermatozoa, as judged from the labelled albumin macrospheres used in HSSG, are rapidly transported into the uterine cavity in the early follicular phase, a marked entry of spermatozoa into the tubes can only be demonstrated during the mid-follicular phase, and this is even more pronounced during the late follicular phase of the cycle. Furthermore, it has been demonstrated that the transport of spermatozoa into the tubes is directed preferentially into the tube ipsilateral to the dominant follicle (Kunz *et al.*, 1996). Within this tube the transport appears to be arrested in the isthmical part where, during the pre-ovulatory phase, a mucous plug is formed (Jansen, 1980), which serves as a secondary sperm reservoir, the cervical mucus being the primary one (Harper, 1994). Thus, passive sperm transport through the female genital tract is under the endocrine control of the dominant follicle with respect not only to the level reached but also to the direction in which the spermatozoa are

Table I. The diameter of the dominant follicle and the oestradiol and progesterone serum concentrations during the menstrual period, the early, mid- and late follicular phases, and the mid-luteal phase of the cycle in patients and controls examined by vaginal sonography for uterine peristalsis (values are means ± SD)

Phase of the cycle	*n*		Follicular diameter (mm)		Serum oestradiol (pg/ml)		Serum progesterone (ng/ml)	
	−	+	−	+	−	+	−	+
During menstruation	7	8	–	–	36.0 ± 31 9	40.0 ± 33.8	0 51 ± 0 55	0 31 ± 0.23
Early follicular	14	13	<11.0	<11.0	28.0 ± 12 8	36.0 ± 21.2	0 45 ± 0 46	0 43 ± 0 12
Mid-follicular	22	17	13 9 ± 1.6	14 1 ± 1 2	63 0 ± 31 1	79 0 ± 38.5	0 35 ± 0 29	0 57 ± 0 81
Late follicular	10	9	18 3 ± 1.4	19 3 ± 3 5	175.0 ± 106.5	180.0 ± 115 9	0 89 ± 1 09	0 80 ± 0.97
Mid-luteal	14	14	–	–	87 0 ± 48 7	104 0 ± 93 0	14 7 ± 3 6	11.3 ± 6.6

− and + indicate patients without and with endometriosis

Table II. The diameter of the dominant follicle and the oestradiol and progesterone serum concentrations during the early, mid- and late follicular phases of the cycle in patients and controls examined by hysterosalpingoscintigraphy (values are means ± SD)

Phase of the cycle	*n*		Follicular diameter (mm)		Serum oestradiol (pg/ml)		Serum progesterone (ng/ml)	
	−	+	−	+	−	+	−	+
Early follicular	7	20	<11 0	<11 0	32 0 ± 10 7	50 0 ± 40.8	0 33 ± 0 21	0 44 ± 0.37
Mid-follicular	11	17	14 4 ± 1 7	14 4 ± 1 5	64 0 ± 31 2	68 0 ± 28 1	0 31 ± 0 24	0 48 ± 0.65
Late follicular	10	16	19 3 ± 3 1	18 8 ± 3 9	208 0 ± 98 4	168 0 ± 92 9	0 46 ± 0 27	0 44 ± 0 31

− and + indicate patients without and with endometriosis

transported (Kunz *et al.*, 1996). It is tempting to speculate that oxytocin and prostaglandins act as mediators in this system of coordinated uterine contractions (Eliasson and Posse, 1960; Hein *et al.*, 1973; Karim and Hillier, 1973; Fuchs *et al.*, 1985; Takemura *et al.*, 1993; Lefebvre *et al.*, 1994a,b), and that the specific architecture of the myometrium plays a significant role in this regard (Goerttler, 1930). The exact mechanisms, however, that govern this system of directed rapid sperm transport, which appears to be of fundamental importance in the process of reproduction, remain to be elucidated.

It is reasonable to assume that the uterine peristaltic pump destined for the transport of spermatozoa during the follicular phase and presumably for securing high fundal implantation of the embryo in the mid- to late luteal phase of the cycle, may also transport other particles, such as bacteria, detached and exfoliated endometrial cells and tissue fragments from lower parts of the genital tract, e.g. the upper vagina or the uterine cavity, into the tubes and even into the peritoneal cavity. While several protective mechanisms impede the ascension of bacteria within the female genital tract, e.g. the acidic milieu of the upper vagina and local and systemic immune reactions, viable endometrial cells and tissue fragments could be transported, unimpeded, from the uterine cavity into the tubes and the peritoneal cavity. Detached endometrial tissue fragments have been shown to be present in the tube, by means of tubal flushing, throughout the menstrual cycle (Bartosik *et al*, 1986; Kruitwagen *et al.*, 1991b). Thus, the mechanism underlying passive sperm transport could be considered, in addition to retrograde menstruation (Sampson, 1925, 1927), as another force responsible for the transport of endometrial tissue into the peritoneal cavity where it might implant and develop into endometriosis.

However, in healthy women with normal menstrual cycles and a normally functioning uterine peristaltic pump, inert particles are virtually only transported up to the level of the uterine cavity during the early proliferative phase of the cycle because of the relatively slow peristaltic activity of the uterus. Moreover, as the follicular phase progresses and with the corresponding increase in power of the peristaltic pump, transport into the tubes and into the peritoneal cavity would eventually occur, although the formation of the isthmical mucous plug in the tubes acts as a barrier for further passive ascension. In oestrous rats only viable spermatozoa could reach the ampullary part of the tubes, while dead spermatozoa and India ink particles were not transported (Leonard and Perlman, 1949). Thus, both a normally functioning peristaltic pump in the early follicular phase and the developing isthmo–tubal mucous plug in the later stages of the follicular phase would, to a large extent, prevent the transport of inert particles such as endometrial cells and tissue fragments beyond the confines of the uterine cavity and the isthmical part of the tubes.

In women with endometriosis, however, uterine peristalsis is increased with nearly double the frequency of peristaltic waves during the early follicular, mid-follicular and mid-luteal phases of the cycle in comparison with healthy women. As a consequence, inert particles are transported beyond the confines of physiological passive sperm transport. The amount of radioactivity measured in compartment 3 during the early follicular phase is increased 3-fold over the corresponding value for healthy women In the mid-follicular phase of the

cycle a peculiar pattern of distribution of the radioactivity within compartment 3 is observed in patients with endometriosis in comparison with healthy women. The total amount of radioactivity in compartment 3 of patients is more than twice as high, and is significantly higher with respect to the tube contralateral to the dominant follicle, as in healthy women. While in healthy women the transport of inert particles is preferentially directed into the tube ipsilateral to the dominant follicle, most of the radioactivity in patients with endometriosis is measured in compartment 3 contralateral to the dominant follicle. We assume that the formation of the mucous plug in the isthmical part of the tubes is asymmetrical in that in the contralateral tube it may be somewhat delayed in comparison with the ipsilateral side as a consequence of presumably higher oestradiol concentrations in the tissue adjacent to the dominant follicle. Therefore we assume that in patients with increased peristaltic activity of the uterus, the mechanism of directed sperm transport is overridden and the inert particles are preferentially pushed into the tube contralateral to the dominant follicle. This is probably why, whenever a massive entrance of radioactivity into compartment 4 during the mid-follicular phase was observed, it occurred via the tube contralateral to the dominant follicle [Figure 3 (2a–c)].

During the late follicular phase of the cycle the peristaltic activity in patients with endometriosis is increased further, but the difference in frequency in comparison with healthy women is less pronounced than in the other phases of the cycle, except during the menstrual period. However, there is no directed transport into the dominant tube. Overall, the distribution pattern of the labelled macrospheres within the three compartments is similar to that observed in the early follicular phase of healthy women despite a 3-fold increase in peristaltic activity. Thus, the efficiency of the system of passive sperm transport is reduced dramatically. This is probably because the peristaltic activity in these patients became more convulsive in character. Some contraction waves started in the middle portion of the uterine cavity, while in other patients the contractions started at different sites at the same time, and some vanished before reaching the fundal part of the uterine cavity. Thus, in comparison with the regular and frequent cervico–fundal contractions of healthy women, the impression of a dysperistalsis prevailed in patients with endometriosis (Kunz and Leyendecker, 1996).

Our data obtained with VSUP demonstrate a rather strict association of uterine hyperperistalsis with endometriosis (Figure 2). As presumably all the women studied (the healthy controls and the subjects with endometriosis) regularly experience retrograde menstruation (Polishuk and Sharf, 1965; Blumenkrantz *et al.*, 1981; Halme *et al.*, 1984), and as the occurrence of endometriosis is largely restricted to patients with hyperperistalsis, we suggest that the development of endometriosis is not so much caused by retrograde menstruation but rather by uterine hyperperistalsis. This corresponds with the results of Bartosik *et al.* (1986), who found a higher incidence of endometrial tissue fragments in peritoneal fluid before and following uterine irrigation in patients with endometriosis compared with controls without endometriosis. Furthermore, in the patients with iatrogenically refluxed endometrial cells, the incidence of finding these cells was higher in the luteal phase than during the follicular phase. Our study demonstrates that uterine hyperperistalsis of patients with endometriosis is also present during the luteal phase.

The increased incidence of endometrial cells within the female genital tract in patients with endometriosis, as shown by uterine irrigation, suggests that uterine hyperperistalsis not only supports the transport of the cells into compartment 4 but may also facilitate the detachment and exfoliation of cells and tissue fragments from the eutopic site. The convulsive dysperistalsis may be especially important in this respect. The detached material would be accumulated inside the uterine cavity in the pre- and peri-ovulatory period and could be transported into the peritoneal cavity during the luteal phase as soon as the isthmic mucous plug has disappeared. By culturing the pellet of peritoneal fluid obtained in the late proliferative phase of the cycle, Willemsen *et al.* (1985) could not identify adhering and proliferating endometrial cells in any of 115 cultures, whereas after uterine tubal irrigation, proliferating endometrial cells were present in 67% of the cultures (Kruitwagen *et al.*, 1991b).

The cervico–fundal peristaltic waves for rapid sperm transport originate at the internal os of the cervical canal, where an apical aliquot of cervical mucus is separated from the remaining mucus (Fukuda and Fukuda, 1994), presumably by a constriction ring that migrates as a peristaltic wave in the fundal direction. It is conceivable that at this narrow site of origin of peristalsis, especially under the condition of hyperperistalsis, the detachment of tissue fragments is particularly facilitated. Furthermore, this may explain why the tissue of endometriotic lesions displays characteristics not only of the eutopic endometrium but also of the tissue of the region of the upper cervical canal, as well as the isthmus uteri with regard to oestradiol receptor distribution and electron microscopical microstructure (Bergquist *et al.*, 1981; Jänne *et al.*, 1981; Schweppe *et al.*, 1984). Recently, it was emphasized that ectopic endometrium displays more or less totally the characteristics of eutopic endometrium with respect to oestrogen and progesterone receptor distribution and expression. By examining almost exclusively ovarian endometriomas, however, the authors have only studied highly selected material (Jones *et al.*, 1995).

There were, on the basis of our as yet limited material, no indications that the degree of hyperperistalsis was related to the stage of endometriosis, the location of the endometriotic implants or the expansion of the endometriotic lesions within a certain grade. Furthermore, preliminary data indicate that hyperperistalsis does not disappear following medical or surgical treatment (G.Leyendecker, unpublished). Thus, there is good evidence that uterine hyperperistalsis is not the consequence of endometriosis but rather the latter's cause.

Retrograde menstruation has long been considered as the mechanism that transports viable endometrial cells into the peritoneal cavity and may therefore be responsible for the development of endometriosis (Sampson, 1925, 1927; Polishuk and Sharf, 1965; Blumenkrantz *et al.*, 1981; Halme *et al.*, 1984; Kruitwagen *et al.*, 1991a,b; Koninckx, 1994). This assumption has at the same time also been questioned by other

authors (Ranney, 1980; Evers, 1994). Retrograde menstruation appears to be a physiological phenomenon because it is observed in nearly all women (Blumenkrantz *et al.*, 1981, Halme *et al.*, 1984). This is underlined by our observation that ~50% of contractions during the later phases of menstruation exhibit a cervico–fundal direction in healthy women. The total number of contractions and the cervico–fundal ones are slightly though insignificantly increased in women with endometriosis. A day to day profile of uterine peristalsis has not yet been established during menstruation. Preliminary data suggest that the proportion of cervico–fundal contractions increases during the menstrual period. However, according to recent data concerning pregnancy rates and the timing of sexual intercourse in relation to ovulation (Wilcox *et al.*, 1995), these early cervico–fundal contractions are most probably not functionally related to sperm transport. It is reasonable to assume that the fundo–cervical contractions prevailing during the early menstrual period enable the vaginal discharge of the majority of desquamated endometrium and that the cervico–fundal contractions increasing in number with the progression of the menstrual period enable, by retrograde menstruation, the preservation of iron content of the body.

Endometriosis is often associated with reduced fertility or infertility However, low grade endometriosis is not considered as a cause in this respect because neither hormonal nor surgical eradication of the endometriotic lesions improves pregnancy rates over untreated controls, even when cyclic function is also optimized (Hull *et al.*, 1986; Adamson and Pasta, 1994). The failure of treatment in this respect is a strong argument against the assumption that the milieu within the cul de sac of patients with endometriosis may impede mechanisms of conception and thus contribute to infertility (Fakih *et al.*, 1987). The success rates in in-vitro fertilization (IVF) and related technologies such as gamete intra-Fallopian transfer (GIFT) do not, by large, differ between patients with and without endometriosis (Alsalili *et al.*, 1995; Dmowski *et al.*, 1995; Kenny, 1995; Olivennes *et al* , 1995; Tanbo *et al.*, 1995) Thus, implantation is not specifically impeded in patients with endometriosis, except possibly those patients with defective uterine receptivity during the implantation phase that cannot be overcome by ovarian stimulation and luteal supplementation (Lessey *et al.*, 1995). Hence, infertility in patients with low grade endometriosis is still enigmatic and considered to be idiopathic.

Our study in patients with endometriosis demonstrates for the first time a dysfunction which may constitute a severe obstacle in the process of reproduction. During the late follicular phase of the cycle, passive sperm transport is impeded dramatically by uterine dysperistalsis, which results in both a reduced aspiration of spermatozoa from the external cervical os into the uterine cavity and a severely impaired directed transport into the tube ipsilateral to the dominant follicle. As judged from HSSG, this results in at least a 3-fold decrease in sperm content in the isthmical mucous plug of the tube ipsilateral to the dominant follicle.

In this context it is of interest that in women with idiopathic sterility, artificial reproductive techniques, such as IVF, GIFT, intraperitoneal insemination (Crosignani *et al.*, 1991) and ovum–sperm transfer (Coulam *et al.*, 1991), are applied successfully. Furthermore, in these women intrauterine insemination yields higher pregnancy rates than timed intercourse (Chung *et al.*, 1995), and intrauterine insemination is surpassed by Fallopian tube sperm perfusion in this respect (Kahn *et al.*, 1993). Thus, there is circumstantial evidence that inefficient sperm transport as a result of uterine dysperistalsis may also be involved in idiopathic or unexplained infertility not associated with endometriosis.

On the basis of our results and the data from the literature, we would like to propose the following concept of the aetiology and pathogenesis of endometriosis.

Uterine peristalsis with cervico–fundal direction has three functions during the menstrual cycle: (i) iron preservation during the later stages of the menstrual period by retrograde menstruation; (ii) directed passive sperm transport from the cervical os and the cervical canal to the isthmical mucous plug of the tube ipsilateral to the dominant follicle; and (iii) high implantation of the embryo (the latter function was brought to our attention by R.G.Edwards in a personal communication).

Although mechanisms are operative that largely prevent ascension and implantation of cells in the peritoneal cavity, such as the fine tuning of the frequency and intensity of physiological uterine peristalsis and the development of the tubo–isthmical mucous plug, it is probably inevitable that, over a period of time, endometrial cells and tissue fragments, which are capable of implantation and further growth, enter the peritoneal cavity. That is why many fertile women develop mostly mild endometriosis, with an increasing incidence in relation to the amount of time elapsed since the last pregnancy (Moen, 1991; Moen and Muus, 1991). Local healing processes may, in addition, control the development of endometriosis (Koninckx, 1994). Endometriosis may develop early and progress to an advanced stage in women whose eutopic endometrium displays an increased cell proliferation (Wingfield *et al.*, 1995). Furthermore, it has been shown that cells from different endometriotic lesions exhibit a varying, sometimes dramatic, potential for proliferation *in vitro* (Gaetje *et al.*, 1995). Thus, the development of endometriosis may not only be influenced by the number of cells transported into the peritoneal cavity, but also by the time component, the healing response capacity of the peritoneum and the properties of the transplanted cells themselves. Therefore, it was suggested that the eutopic endometrium in endometriosis should become a topic of research (Wingfield *et al.*, 1995). The property of the eutopic endometrium with regard to the increased potency of cell proliferation may be an inheritable quality. Thus, when reproduction occurs early enough during the reproductive lifetime, heritable aspects may become involved in the pathogenesis of endometriosis (Malinak *et al.*, 1980; Simpson *et al.*, 1980).

Uterine hyperperistalsis augments the transtubal transport of inert particles into the peritoneal cavity and may, in addition, promote the detachment of endometrial cells from the eutopic endometrium. This process may start during the later stages of menstruation (Salamanca and Beltran, 1995) and continue throughout the whole cycle. It may even be present in amenorrhoeic states, provided that the concentrations

of oestradiol are high enough not to prevent uterine peristaltic activity. Thus, by this dysfunction the number of endometrial cells that gain access to the peritoneal cavity is increased. This causes a strong association between the incidence of uterine hyperperistalsis and the incidence of endometriosis. Therefore, uterine hyperperistalsis constitutes, in our opinion, the principal mechanical factor for the development of endometriosis. The proliferative potential of the transplanted cells (Gaetje *et al.*, 1995; Wingfield *et al.*, 1995), as well as the peritoneal response, may determine the severity of the disease.

In conclusion, with uterine hyper- and dysperistalsis we have disclosed a new dysfunction within the process of reproduction which might contribute to the development of infertility and, mainly, mild endometriosis. On the basis of the strong association between the occurrence of hyperperistalsis, which results in the transport of inert particles beyond the confines of physiological passive sperm transport, and the occurrence of endometriosis, we suggest that it is not retrograde menstruation (which occurs in all women with patent tubes) but rather uterine hyperperistalsis which constitutes the major mechanical cause of endometriosis, with the dysperistalsis and impeded sperm transport in the pre-ovulatory period being responsible for the reduced fertility.

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