Article

Control and function of uterine peristalsis during the human luteal phase

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Abstract

Rhythmic peristaltic contractions of the muscular wall of the non-pregnant uterus can be demonstrated throughout the menstrual cycle, with a maximum just before ovulation. However, not only during the follicular phase but also during the luteal phase, the uterus shows remarkable contractile activity. The present study was conducted in order to examine uterine peristaltic activity and its function during the luteal phases of the human menstrual cycle. The results of vaginal sonography of uterine peristalsis, of hysterosalpingoscintigraphy and of the documentation of the sites of embryo implantation in natural and artificial cycles have shown that uterine peristalsis during the luteal phase is controlled by systemic and probably even more by local hormonal secretion from the fresh corpus luteum, and facilitates the fundal implantation of the blastocyst predominantly ipsilateral to the site of the dominant ovarian structure. Furthermore, this study suggests that the defence against the infiltration and inflammation of the upper genital tract, and thus the degradation of the implanted embryo, represents a further and phylogenetically old and genuine function of the archimetra, which in placentalia was modified in order to participate in the control of invasion of the endometrium by the trophoblast.

Keywords: *embryo transport, implantation, uterine peristalsis*

Introduction

The non-pregnant uterus is far from a quiescent organ with functions only confined to the preparation of the endometrium for blastocyst implantation. It has gained wide acceptance that uterine peristaltic activity, visualized by means of vaginal sonography of uterine peristalsis (VSUP) during the follicular phases of the menstrual cycle, provides sustained and directed sperm transport, since radiolabelled albumin macrospheres of sperm size migrated from the vaginal depot through the uterus predominantly into the Fallopian tube ipsilateral to the dominant follicle (Kunz *et al.*, 1996, 1997; Leyendecker *et al.*, 1996; Wildt *et al.*, 1998). Uterine peristalsis, and thus directed sperm transport during the follicular phases, are controlled by the oestradiol secretion of the dominant follicle systemically and into the utero–ovarian countercurrent system and is enhanced by oxytocin (Kunz *et al.*, 1998b,c; Wildt *et al.*, 1998). Beyond ovulation the uterine peristaltic activity decreases in frequency and intensity, mainly as a consequence of the rising progesterone secretion as an inhibitor of uterine contractility, but does not disappear (Lyons *et al.*, 1991; Leyendecker *et al.*, 1996; Ayoubi *et al.*, 2001; Fanchin *et al.*, 2001).

While uterine peristalsis serves directed sperm transport during the mid- and late-follicular phases, the function of luteal phase uterine contractions remains almost unknown. It seems conceivable that in humans uterine peristaltic activity during the luteal phase of the menstrual cycle controls embryo implantation (Kunz *et al.*, 1998a,b). Knowledge is still scanty about how the orientation of the human blastocyst towards the site of implantation within the uterine cavity is brought about (Harper, 1994). After entering

the uterine cavity around 4 days following ovulation, the human blastocyst remains in the high fundal part of the uterus without any close contact with the endometrium for about 2 days (Harper, 1994). In many mammals, the orientation of the blastocyst is not random but species-specific (Lee *et al.*, 1977; Thorbert *et al.*, 1978; Stuckhardt *et al.*, 1981, Pope *et al.*, 1982a,b, 1986; Rogers *et al.*, 1983; Baird and Birney, 1985; Dziuk, 1985; Rahima and Bruce, 1986; von Domarus *et al.*, 1986; Legrand *et al.*, 1987, 1989; Wiebold and Becker, 1987; Louton *et al.*, 1988; Nephew *et al.*, 1989, 1992).

By means of VSUP, hysterosalpingoscintigraphy (HSSG) and with the determination of the sites of embryo implantation using vaginal sonography (VS), control and function of luteal phase uterine peristalsis have been examined. The data provide strong evidence that luteal phase uterine contraction waves are controlled by the dominant corpus luteum and play an important role in the control of human embryo implantation.

Materials and methods

Patients

A total of 490 healthy women aged 21–46 years (mean 31) with proven fertility (i.e. parous women) or suffering from andrological sterility including 61 women suffering from mostly low grade endometriosis and infertility (studies 1, 2, 3, 4, 7, 8) or with spontaneously conceived ongoing early pregnancies (study 5) or suffering from missed abortions following spontaneous conceptions (study 6) entered the studies after giving informed consent. In all patients in studies 1–4, 7 and 8, laparoscopies had been performed previously and all 490 patients experienced regular and ovulatory cycles. By means of vaginal sonography, the present menstrual cycle of all patients in studies 1, 2, 4, 7 and 8 was observed during the follicular phases in order to document normal follicular development and localization as well as ovulation preceding the luteal phase. The assignment to the respective phases of the menstrual cycles occurred according to the results of hormone measurements and to the sonographical documentation of the dominant ovarian structure. Furthermore, the site of the corpus luteum was documented by means of vaginal sonography (Logiq 500; Kranzbühler, Solingen, Germany). Women with a history of ovariectomy, uterine fibroids (Gianaroli *et al.*, 2005), malformations, ectopic pregnancies or irregular menstrual cycles were excluded from the studies.

Aims of studies

Studies 1–3 examined the patterns of uterine peristalsis under different endocrinological situations, especially during the luteal phases of the human menstrual cycle in order to document differences.

The mucus of the uterine cervix during the luteal phase is widely considered as a barrier against the ascension of spermatozoa or other particles of the same size. Furthermore, the uterine peristaltic activity subsequent to ovulation appears rather weak. By means of HSSG as shown in study 4, new insights were gained into the directed transport capacity provided by uterine peristalsis during the luteal phase.

Studies 5–8 were performed to examine the physiology and pathophysiology of intrauterine migration of the human embryo prior to implantation.

Study 1: VSUP in normal cycles

By means of VSUP in 77 healthy women and in 61 women suffering from mostly low grade endometriosis and infertility, the frequency and pattern of the uterine peristaltic activity during the menstrual, early-, mid- and late- follicular as well as in the midluteal phases of their cycles (span: day 18 to day 22 of the cycles, mean: day 20) were examined and published by the study group (Leyendecker *et al.*, 1996; Kunz *et al.*, 1997). The video documentations of uterine peristalsis in this subgroup of patients were reanalysed. Furthermore, VSUP was performed in five healthy women during the late-luteal phases (span: day 25 to day 27 of the cycles, mean: day 26) of their regular cycles.

Study 2: VSUP in artificial cycles

Thirteen women received daily, orally administered oestradiol valerate (Progynova®; Schering AG, Berlin, Germany) following pituitary down-regulation with triptorelin (Decapeptyl-Depot®; Ferring Arzneimittel GmbH, Kiel, Germany) administered during the midluteal phase of the preceding cycle. Oestradiol valerate was administered at doses of 4 mg for days 1–3, of 6 mg for days 4–9 and of 8 mg for days 10–15 in order to prepare the endometrium for embryo transfer following cryopreservation of pronuclear stage oocytes. Oestradiol valerate administration was reduced to 4 mg for days 16–30. Starting with 200 mg of progesterone (Utrogestan®; Dr Kade/Besins Pharma GmBH, Berlin, Germany) in the evening of day 15, 600 mg of progesterone per day was administered intravaginally on days 16–30.

Vaginal sonography of uterine peristalsis (VSUP) was performed on day 22, representing the midluteal phase, and on day 28, representing the late-luteal phase of the artificial cycle, respectively.

The results of the VSUP obtained from the follicular phase have been published (Kunz *et al.*, 1998c), but the video records were re-analysed.

Study 3: VSUP in stimulated cycles

Twenty women achieved supraphysiological concentrations of endogenous oestradiol in ovarian stimulation cycles for assisted reproductive technology. These women were treated with human menopausal gonadotrophins (Menogon®; Ferring Arzneimittel GmbH) at mean daily doses of 225 IU of FSH and 225 IU of LH respectively, following pituitary down-regulation with triptorelin (Decapeptyl-Depot®; Ferring Arzneimittel GmbH) according to the long protocol (Leyendecker *et al.*, 1990). VSUP was performed on days +9 and +15 days following the administration of human chorionic gonadotrophin (HCG, Choragon®; Ferring GmBH), corresponding to the mid and late-luteal phase in normal cycles, respectively. The results of follicular phase uterine activity have been published (Kunz *et al.*, 1998c), but the video records were reanalysed.

Study 4: hysterosalpingoscintigraphy (HSSG)

Between 1994 and 1996, HSSG was performed in nine women during the luteal phases of the regular cycles (between day 18 and day 26 of the menstrual cycle, mean day 21 of cycle) according to the methods described (Kunz *et al.*, 1996). In addition, HSSG was performed in 64 women during their follicular phases. The results of the HSSG obtained from women during the follicular phases of the menstrual cycles have been published (Kunz *et al.*, 1996; Leyendecker *et al.*, 1996). For the present study, the HSSG documents obtained from women in the luteal phase were reanalysed.

The ascension of the aliquot of labelled albumin macrospheres of sperm size from the site of application in the dorsal fornix of the vagina through the uterine cavity up to the Fallopian tubes was documented by a gamma camera (Orbiter; Siemens, Erlangen, Germany), providing serial anterior–posterior scintigrams until the 32nd minute after application. For assessment of ascension, the genital tract was subdivided into three compartments. The site of application was compartment 1, the uterine cavity was compartment 2 and the Fallopian tubes were compartment 3. Regions of interest within compartments were determined and the counts within each compartment were measured and calculated as percentage of the total measured radioactivity (for further details, see Kunz *et al.*, 1996). The patients were advised not to conceive during an HSSG cycle and thus no conceptions occurred.

Study 5: early gestational sacs in spontaneous ongoing pregnancies

In 30 healthy women with ongoing single pregnancies following spontaneous conceptions the localization of the early gestational sacs within the uterine horns of the high fundal part of the uterus were determined by means of high resolution vaginal sonography. The localization was then related to the site of the corpus luteum of pregnancy and described as localized ipsilaterally, centrally or contralaterally. The investigations were performed between gestational weeks 5 and 7.

Study 6: early gestational sacs in spontaneous missed abortions

By means according to study 5, the localization of the gestational sac in relation to the site of the corpus luteum of pregnancy was evaluated in 23 healthy women suffering from missed abortions following spontaneous conceptions. Vaginal scans were performed during weeks 5–8 of gestation. Subjects exhibiting vaginal bleeding, pelvic pain or opening of the external cervical os, or demonstrating myometrial contractions as obtained by VSUP, were excluded from the study, as well as women with multiple pregnancies.

Study 7: early gestational sacs in assisted reproduction cycles with fresh embryo transfer

A total of 118 healthy women entered this prospectively designed study. All subjects achieved supraphysiological concentrations of endogenous oestradiol in ovarian stimulation cycles for artificial reproductive technology as described in study 3. The embryo transfers were performed 2 days subsequent to oocyte retrieval. One to three embryos were transferred into the uterine cavity according to the German Embryo Protection Law. Surplus pronuclei stage oocytes were cryopreserved.

A curved catheter guide (Labotect GmbH, Göttingen, Germany) was used for ET. This type of catheter was originally used for performing transvaginal embryo transfer into the isthmical part of the Fallopian tube (embryonal intra-Fallopian tube transfer, EIFT). The curved shape, its markings and its flexibility as well as the way of insertion allowed placing of the tip of the guide within one selected uterine horn. The transfer catheter itself was introduced into the guide and surpassed the tip of the guide by about 5 mm.

The transfer catheter was adjusted and all embryos of each patient were transferred alternately either into the left or right cornual section of the uterine cavity. In cases of ongoing early pregnancies between weeks 5 and 7 of gestation with respect to the day of oocyte retrieval, the localization of the gestational sacs were documented sonographically and related to the left or right cornual section of the uterine cavity or described as being located centrally by a second investigator, who had had no previous information about the primary site of embryo deposition during embryo transfer.

Study 8: early gestational sacs following directed transfer of frozen–thawed embryos in artificial cycles with exogenous steroids

Applying the same means as in study 7, the localization of the gestational sacs following directed transfer of frozen–thawed embryos in artificial cycles with exogenous steroids and without a dominant ovarian structure in 135 healthy women were documented. The sequential administration of oestrogens and gestagens following hypophyseal down-regulation was performed as described in study 2. The cryopreserved pronuclei stage oocytes were thawed on day 16 of the cycle and were transferred as described in study 7 on day 17 of the artificial cycle.

Vaginal sonography of uterine peristalsis (VSUP)

VSUP was performed with a 7.5 Mhz probe (Logiq 500; Kranzbühler, Solingen, Germany) as previously published (Kunz *et al.* 1996; Leyendecker *et al.*, 1996). The probe was placed in a position to yield a sagittal section of the whole uterus and was kept in a fixed position over a period of 5 min. The whole scan was videotaped for quantitative assessment of uterine peristalsis. In order to obtain a good estimation of the frequency of the contraction waves the tape was replayed at 5 times regular speed. This also allowed the direction of the waves to be determined. Waves starting in the isthmical part of the uterus and continuously migrating to the upper fundal myometrium were described as cervico–fundal or type A contractions, while type B contractions were fundo–cervical in direction. If a contraction wave started in the isthmical part of the uterus but did not surpass the isthmical region or lower fundal myometrium it was characterized as

isthmical or type C contraction wave.

Hormone measurements

From each woman, a venous blood sample was drawn for the measurement of the serum oestradiol, progesterone and LH concentrations, using a commercially available radioimmunoassay kit (Serono Diagnostics GmBH, Freiburg, Germany).

Statistical analysis

Statistical analysis was performed using Student's *t*-test, chi-squared test and determination of the coefficient of correlation and significance was assumed when $P < 0.05$.

Results

Patients

In all patients in studies 1 and 4, an ovulatory menstrual cycle could be documented. The women in studies 3 and 7 experienced transvaginal follicular aspiration 36 h after the administration of 10,000 IU HCG. No follicular development, and thus formation of a corpus luteum, could be observed in the women in studies 2 and 8.

The results of studies 1–3 are presented graphically and in tabular form below. **Figure 1** presents serial scintigrams obtained by HSSG from a woman on day 22 of her regular menstrual cycle. **Figure 2** depicts the distribution of the percentage of total counts,

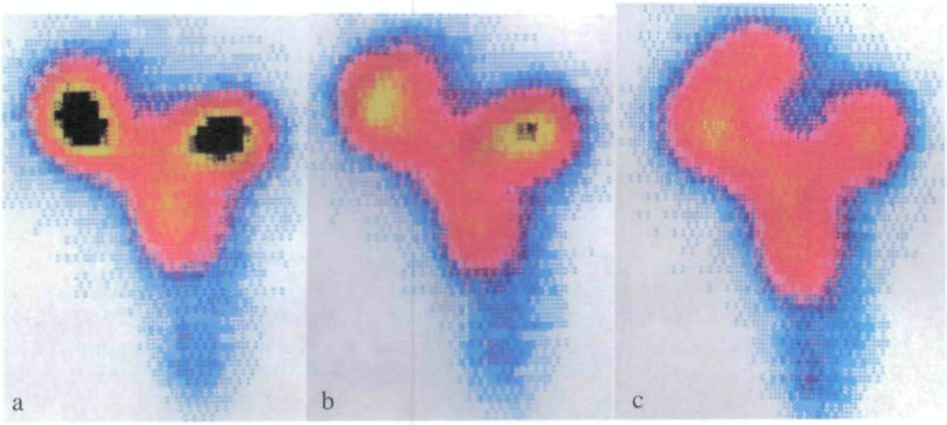

Figure 1. Representative scintigrams obtained by hysterosalpingoscintigraphy in a single patient during the midluteal phase. Scintigrams obtained 1 (**a**), 16 (**b**) and 32 (**c**) min after vaginal application of the radiolabelled macrospheres are shown. The fresh corpus luteum was located in the right ovary.

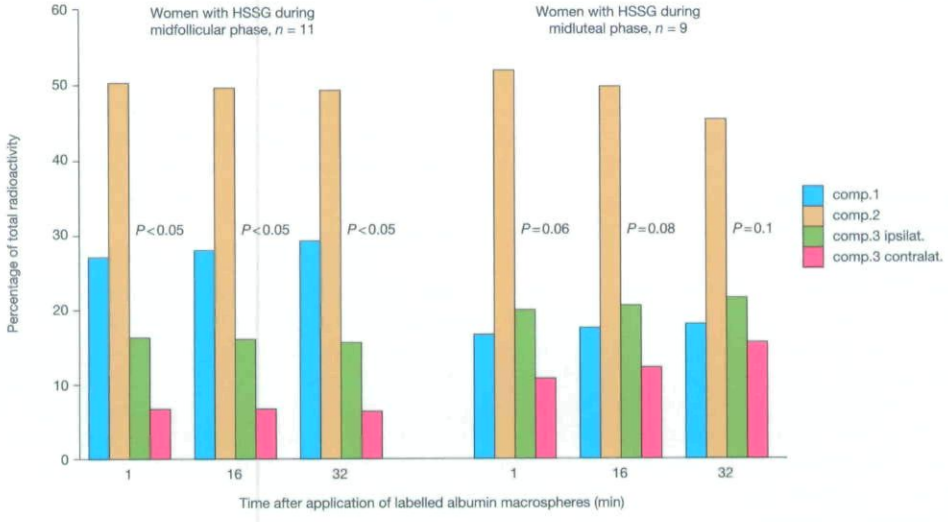

Figure 2. The distribution of the percentage of total counts, representing the labelled albumin macrospheres, within the female genital tract (compartments 1, 2 and 3 being the upper vagina, the uterine cavity and the isthmical part of the tubes, respectively) following 1, 16 and 32 min after vaginal application during the midfollicular (left half) and the midluteal (right half) phases of the normal cycles. With respect to compartment 3, the right and left tubes were differentiated. While the amount of radioactivity transported into the tubes ipsilateral to the dominant ovarian structure as compared with the contralateral tube was significantly higher during the mid-follicular phases ($P < 0.05$), the respective differences just failed significance during the mid-luteal phases. However, an apparent similarity of the relative distribution of the macrospheres within the uterine compartments between both groups of patients can be seen, with an orientation of the inert particles towards the tube ipsilateral to the localization of the dominant ovarian structure also during the mid-luteal phases of the cycles. HSSG = hysterosalpingoscintigraphy.

representing the labelled albumin macrospheres within the female genital tract during the midluteal phases of the cycles as compared with the corresponding results obtained from healthy women during the midfollicular phases as documented previously (Kunz *et al.*, 1996; Leyendecker *et al.*, 1996).

Study 1

The reanalysis of the VSUP during the follicular phases of the menstrual cycles of healthy women and of women with endometriosis confirmed the previously published results (Kunz et al., 1996, 1997; Leyendecker et al., 1996). Uterine peristalsis during the follicular phases comprised type A and B contraction waves, while no type C contractions could be observed. Patients suffering from endometriosis exhibited significantly increased peristaltic activity as compared with the healthy controls (patients characteristics, apart from the endometriosis, were comparable to the controls; for details, see Leyendecker et al., 1996). During the late-follicular phase the increased peristaltic activity in women suffering from endometriosis attained the character of dysperistalsis as compared with the healthy women.

However, during the mid- and late-luteal phases, a different pattern of uterine peristalsis was obtained as compared with the uterine peristaltic activity during the follicular phases, as well as compared with the results of midluteal phase VSUP as previously published (**Figure 3**) (Leyendecker *et al.*, 1996; Kunz *et al.*, 1997).

Beyond ovulation, type B contractions almost disappeared while isthmical or type C contractions appeared as a new pattern of peristaltic activity. During the midluteal phases of the healthy women, the frequency of type C contractions was significantly higher with 2.1 contractions/min (SEM: 0.16) compared with 1.1 contractions/min (SEM: 0.14) of type A contractions ($P < 0.05$). Hence the ratio of type C to type A frequency (CA ratio) of contraction waves was 1.9:1. Since almost every contraction observed during the midluteal phases started in the isthmical pacemaker region and not in the high fundal myometrium, the relation of 1.9:1 means that roughly every second wave generated in the isthmus migrated towards the uterine fundus. During the late luteal phases type C wave frequency was 1.6 contractions/min (SEM: 0.17) and type A wave frequency was 0.44 contractions/min (SEM: 0.24), therefore increasing the CA ratio to a value of 3.6:1. While the decrease in type A activity from the mid- to the late-luteal phases was statistically significant ($P < 0.05$), type C uterine peristalsis did not change significantly with the progression of the luteal phases. Further statistic calculations revealed a highly significant negative coefficient of correlation of type C with –0.77 ($P < 0.0005$) and type A contraction frequencies with –0.6 ($P < 0.005$) with the corresponding oestradiol serum concentrations during the midluteal phases of the healthy women (**Table 1**). A positive coefficient of correlation existed during the late-luteal phases between type C and type A uterine activity and the serum concentrations of oestradiol and progesterone, respectively. While the correlation between serum progesterone and type C activity was statistically significant (coefficient: 0.93; $P < 0.005$), the correlation between type C wave frequency and oestradiol concentrations just failed significance (coefficient: 0.75, $P = 0.06$). No significant correlation between type A activity and the serum concentrations of the sex steroids could be obtained during the late luteal phases of healthy women.

Patients with endometriosis showed a type C frequency of 3.04 contractions/min (SEM: 0.16) and a type A frequency of 2.17 contractions/min (SEM: 0.21) during the midluteal phases, with a calculated CA ratio of 1.4: 1 (**Figure 4**). Furthermore, the mean isthmical as well as the mean fundal frequency of uterine contractile activity differed significantly from the respective values obtained from the healthy control group ($P < 0.0002$). Type A and C contractions prevailed with more than 90% of all waves. No significant correlations between the particular uterine frequencies and the serum concentrations of oestradiol and progesterone could be obtained.

Study 2

Oestradiol valerate and progesterone administration resulted in oestradiol and progesterone serum concentrations similar to those of the normal follicular (Kunz *et al.*, 1998c) and midluteal phases of the menstrual cycle respectively. However, during the late-luteal phases, sex steroid concentrations were more than doubled in women receiving exogenous sex steroids as compared with the control (**Table 2**).

Re-analysis of uterine peristaltic activity during the first half of the artificial cycles with oestradiol valerate administration only, thus mimicking the follicular phase, showed no differences as compared with published results (Kunz *et al.*, 1998c).

The frequency of peristaltic waves during the midluteal phases paralleled those in normal cycles with a mean of 2.2 contractions/min (SEM: 0.25) in the isthmical part (type C) and a mean of 1.1 contractions/min (SEM: 0.2) in the high fundal part (type A) of the uterus. The CA ratio could be calculated as 2:1. However, from the mid- to the late-luteal phase type C wave frequency decreased non-significantly to 1.9 contractions/min (SEM: 0.16), while type A activity decreased highly significantly to 0.2 contractions/min (SEM: 0.07) ($P < 0.0001$), changing the CA ratio to a value of 9.7:1.

The only significant coefficient of correlation could be observed during the midluteal phase with 0.62 between the serum concentrations of oestradiol and type C wave activity ($P < 0.05$). The percentage of type A and C contractions exceeded 95%.

Study 3

The stimulation of ovarian function with human menopausal gonadotrophin (HMG) resulted in supraphysiological concentrations of serum oestradiol and progesterone during the follicular (Kunz *et al.*, 1998c) and luteal phases of the cycles (**Table 3**), which differed significantly from those of normal cycles, on the basis of the day of cycle (in study 1) and of the days preceding or following HCG administration (in HMG cycles) respectively.

The reanalysis of uterine peristaltic activity during the follicular phases demonstrated no differences as compared with the results published (Kunz *et al.*, 1998c).

During the midluteal phases of the stimulation cycles, the mean isthmical or type C frequency of uterine contractions was 1.6 contractions/min (SEM: 0.26) and 0.7 contractions/min (SEM: 0.18) for type A activity revealing a CA ratio of 2.4:1. With

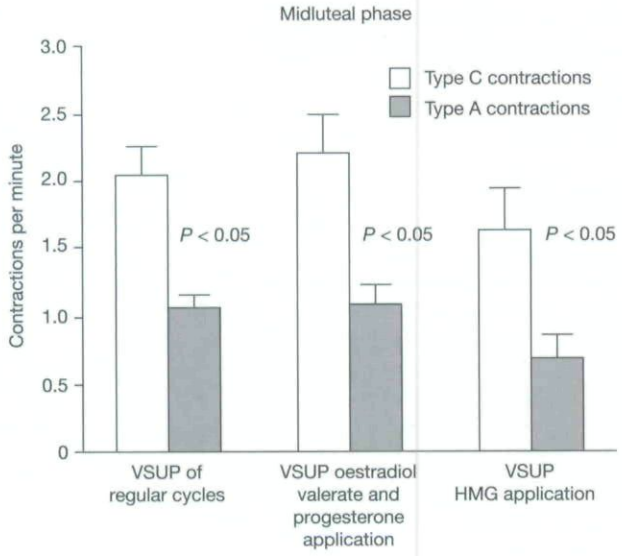

Figure 3. Graphical representation of the frequency of the subendometrial uterine peristaltic waves (means ± SEM contractions/min) during the midluteal phases of normal menstrual cycles and in women receiving a daily oral dose of oestradiol valerate and progesterone following down-regulation with a gonadotrophin-releasing hormone analogue and in women treated with human menopausal gonadotrophin (HMG) for ovulation induction. The frequency of type A as well as of type C contractions, the latter comprising uterine contractions confined to the isthmical and lower fundal pacemaker region of the uterus, was not significantly different between the investigated groups of subjects. The percentage of cervico-fundal directed waves exceeded 90%. VSUP = vaginal sonography of uterine peristalsis.

Table 1. Diameter of the dominant follicle and oestradiol and progesterone serum concentrations during the menstrual period, the early-, mid- and late- follicular phases, and the mid- and late luteal phases of the cycle in women with and without endometriosis examined by vaginal sonography of uterine peristalsis (VSUP).

Phase of cycle	*No of. women*		*Follicular diameter (mm)*		*Serum oestradiol (pg/ml)*		*Serum progesterone (ng/ml)*	
	–	+	–	+	–	+	–	+
Menstrual	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
Midfollicular	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
Midluteal	14	14	–	–	87.0 ± 48.7	104.0 ± 93.0	14.7 ± 3.6	11.3 ± 6.6
Late luteal	5	–	–	–	50.0 ± 34.7	–	6.0 ± 2.2	–

Values are means ± SD; – and + indicate patients without and with endometriosis.

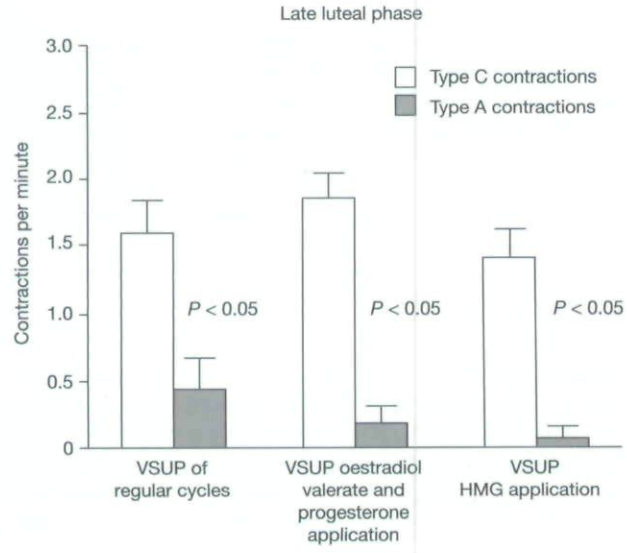

Figure 4. Graphical representation of the frequencies of the subendometrial uterine peristaltic waves (means ± SEM contractions/min) during the late-luteal phases of normal menstrual cycles and in women receiving a daily oral dose of oestradiol valerate and progesterone following down-regulation with a gonadotrophin-releasing hormone analogue and in women treated with human menopausal gonadotrophin (HMG) for ovulation induction. The mean frequencies of type C contractions did not differ statistically from the corresponding frequencies observed during the midluteal phases. However, in all groups studied the mean frequencies of type A uterine contraction waves decreased significantly from the mid- to the late-luteal phase and were significantly different between the separate groups of women during the late-luteal phases. The percentage of cervico-fundal directed waves exceeded 90%. VSUP = vaginal sonography of uterine peristalsis.

Table 2. Oestradiol and progesterone serum concentrations during the early, mid- and late-follicular phases and during the mid- and late-luteal phases of the cycles in patients investigated with vaginal sonography of uterine peristalsis (VSUP) following oestradiol valerate and progesterone application.

Phase of cycle	*No. of women*	*Follicular diameter (mm)*	*Serum oestradiol (pg/ml)*	*Serum progesterone (ng/ml)*
Early follicular	13	–	83 ± 37	0.3 ± 0.3
Midfollicular	13	–	142 ± 59	0.4 ± 0.35
Late follicular	13	–	229 ± 188	0.3 ± 0.25
Midluteal	9	–	74 ± 59	15.8 ± 4.8
Late luteal	13	–	131 ± 95	13.5 ± 6.3

Values are means ± SD.

Table 3. Diameter of the dominant follicle and the oestradiol and progesterone serum concentrations during the early, mid- and late-follicular phases and during the mid- and late-luteal phases of the cycles in patients investigated with vaginal sonography of uterine peristalsis (VSUP) following gonadotrophin application.

Phase of cycle	*No. of women*	*Follicular diameter (mm)*	*Serum oestradiol (pg/ml)*	*Serum progesterone (ng/ml)*
Early follicular	20	<11	119 ± 43	Not measured
Midfollicular	20	13 ± 1.2	571 ± 485	Not measured
Late follicular	20	19 ± 1.8	1435 ± 1156	Not measured
Midluteal	12	–	1519 ± 1171	96 ± 17
Late luteal	12	–	1113 ± 990	36 ± 30

Values are means ± SD.

progression to the late-luteal phase, the type C wave frequency decreased non-significantly to a mean of 1.4 contractions/min (SEM: 0.2), but the frequency of type A contractions decreased significantly to a mean of 0.1 contractions/min (SEM: 0.05, $P < 0.003$) and thus changing the a CA ratio to 20.3:1 (**Figure 5**).

The only significant coefficient of correlation could be observed during the midluteal phase, with 0.5 between the serum concentrations of oestradiol and the type A wave activity ($P < 0.05$). The percentage of type A and C contractions exceeded 95%.

Studies 1–3

Only during the late-luteal phase were the mean frequencies of type A uterine contraction waves significantly different between the study groups.

However, no significant differences could be observed for the mean frequencies of type A waves during the midluteal phases and for type C contractile activities during the mid- and late-luteal phases between the study groups 1–3.

In all women studied, the investigators gained the impression that each peristaltic contraction lost intensity when approaching the fundus of the uterine myometrium, as with a wave running out on a beach. In addition, the intensity of the high fundal or type A contraction waves decreased with the progression of the luteal phase, as judged subjectively from the extent of bending of the approximately oval shaped endometrial lining by a contraction wave.

Study 4: HSSG

While **Figure 1** presents serial scintigrams obtained by HSSG from a woman on day 22 of her regular menstrual cycle, **Figure 2** depicts the findings of the present study provided by HSSG obtained from the midluteal phases of the cycles in comparison with the corresponding results previously obtained from HSSG performed during the midfollicular phases of the cycles (Kunz

et al., 1996). The mean distributions of the percentages of total counts (representing the labelled albumin macrospheres) within the female genital tract are shown 1, 16 and 32 min after vaginal application. **Table 4** presents the mean values of follicular diameter, oestradiol and progesterone serum concentrations.

The midluteal migration of the macrospheres from the vaginal depot through the uterine cavity up to the Fallopian tubes is similar to the ascension observed during the midfollicular phases. Hence considerable radioactivity could be documented in compartment 2 and again a marked ascension into compartment 3 was found. An orientation of the labelled albumin particles towards the isthmical parts of the tubes ipsilateral to the site of the dominant structure occurred. However, in contrast to the findings obtained from the midfollicular phases the increased accumulation of labelled macrospheres of sperm size within the tube ipsilateral to the dominant ovarian structure just failed significance when compared with the mean radioactivity within the contralateral side (after 1st min, $P = 0.055$, after 16th min, $P = 0.078$, after 32nd min, $P = 0.12$).

Study 5

Twenty-five of 29 gestational sacs were been observed within the uterine horn ipsilateral to the corpus luteum of pregnancy, one was detected centrally and three contralaterally. The site of the corpus luteum of pregnancy was documented by means of vaginal sonography in each patient. Thus, significantly more embryos implanted ($P < 0.05$) ipsilateral to the ovary bearing the corpus luteum as compared with the incidence of central or contralateral implantation.

Study 6

Six of 21 gestational sacs were observed ipsilateral, three central and 12 contralateral to the site of the corpus luteum of pregnancy, the latter being visualized in each woman. The difference between ipsilateral and contralateral implantation was statistically significant ($P < 0.02$).

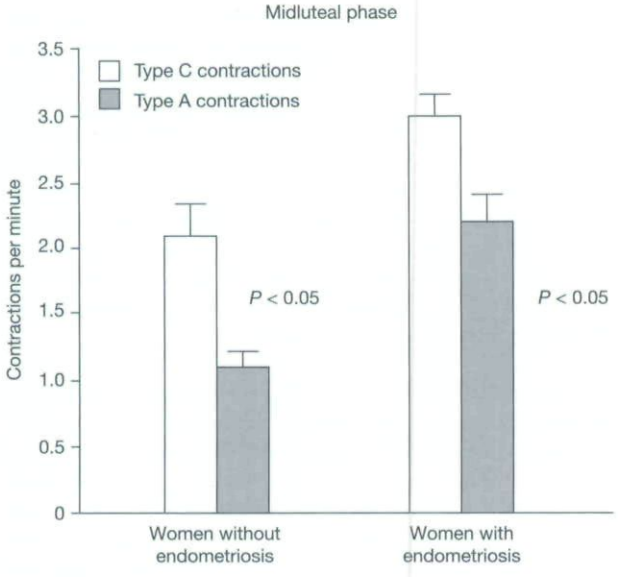

Figure 5. Graphical representation of the mean frequencies of subendometrial uterine peristaltic waves (means ± SEM contractions/min) during the midluteal phases in women with and without endometriosis. The frequencies of type C as well as of type A peristaltic waves differed significantly between both groups of patients. The percentage of cervico-fundal directed waves exceeded 90% in both groups.

Table 4. Diameter of the dominant follicle and the oestradiol and progesterone serum concentrations during the midfollicular and the midluteal phases of the cycle in healthy women examined by hysterosalpingoscintigraphy (HSSG).

Phase of cycle	n	*Follicular diameter (mm)*	*Serum oestradiol (pg/ml)*	*Serum progesterone (ng/ml)*
Midfollicular	11	14.4 ± 1.7	64.0 ± 31.2	0.31 ± 0.24
Midluteal	9	–	75.3 ± 26.7	13.6 ± 3.2

Values are means ± SD.

Study 7

In general, three embryos were transferred (mean 2.8, SD ± 0.5) at the 2–8-cell stage (mean 4.3, SD ± 1.5). Twenty-four of 38 gestational sacs in 29 women developed within the uterine horn into which the embryos were transferred primarily. Seven sacs were located centrally and seven contralaterally. Significantly more embryos implanted within the uterine horn into which they were transferred primarily as compared with the contralateral side ($P < 0.001$). All women in this study demonstrated multiple corpora lutea in both ovaries during the time of embryo transfer and the determination of the early gestational sacs.

Study 8

As in study 7, usually three embryos were transferred (mean 2.8, SD ± 0.4) at the 2–8-cell stage (mean 2.8, SD ± 1.1). Seven of 18 gestational sacs were found ipsilaterally, two centrally and nine contralaterally. There were no statistically significant differences. None of the subjects in study 8 demonstrated a fresh corpus luteum.

In all women in studies 5–8, no gestational sacs within the lower or isthmical region of the uterine cavity were observed.

Discussion

Video sonography of uterine peristalsis (VSUP) (Birnholz, 1984; Oike *et al.*, 1988; Abramovicz and Archer, 1990; De Vries *et al.*, 1990; Lyons *et al.*, 1991; Ijland *et al.*, 1996; Kunz *et al.*, 1996; Leyendecker *et al.*, 1996; Bulletti *et al.*, 2000, 2002; Ayoubi *et al.*, 2001, 2003; de Ziegler *et al.*, 2001; Fanchin *et al.*, 2001; Ayoubi and Fanchin, 2002; Van Gestel *et al.*, 2003; Nakai *et al.*, 2004; Bulletti and de Ziegler, 2005) and HSSG (Itturalde and Venter, 1981; Becker *et al.*, 1988; Steck *et al.*, 1991; Kunz *et al.*, 1996; Leyendecker *et al.*, 1996; Wildt *et al.*, 1998) allow the study of uterine peristaltic activity and utero–tubal transport *in vivo* without stress and injury. Results from VSUP and HSSG indicated that the non-pregnant uterus is far from a quiescent organ and that during the mid- and late-follicular phases of the menstrual cycles the uterine peristaltic pump provides directed sperm transport with the preferential accumulation of the spermatozoa within the tube ipsilateral to the dominant follicle (Kunz *et al.*, 1996; Leyendecker *et al.*, 1996; Wildt *et al.*, 1998).

Luteal phase subendometrial contraction waves have been described as decreasing in frequency and intensity with the progression of the secretory phase and as being directed predominantly from the cervical canal to the fundal part of the uterus (Araki, 1982; De Vries *et al.*, 1990; Oike *et al.*, 1990; Crane and Martin, 1991; Lyons *et al.*, 1991; Leyendecker *et al.*, 1996; Bulletti *et al.*, 2000; Van Gestel *et al.*, 2003; Nakai *et al.*, 2004). However, only scant information exists about the control and function of uterine peristalsis during the luteal phases of the human menstrual cycle. With regard to follicular phase uterine peristalsis providing rapid and directed sperm transport (Kunz *et al.*, 1996), it seems conceivable that uterine peristalsis during the luteal phase might control intrauterine migration of the preimplantation embryo and eventually the site of implantation. However, in contrast to the mechanisms of directed sperm transport, luteal phase uterine contractions encounter additional problems such as tubal regurgitation of the blastocyst or the implantation within lower uterine segments of the uterus resulting in placenta praevia or malnutrition of the conceptus. Therefore, it seems very likely that uterine peristaltic activity during the secretory phases differs in many respects from follicular phase uterine contractions.

Follicular phase uterine peristalsis comprises cervico-fundal or type A and fundo-cervical or type B contractions (Kunz *et al.*, 1996; Leyendecker *et al.*, 1996). This means that each contraction wave initially starting in the fundal or isthmical part of the uterus migrates towards the opposite end. The present study has shown that in addition to type A and B contractile activities, a new type of uterine peristaltic contraction appears during the luteal phase. It starts like a type A contraction wave but does not surpass the isthmical and lower fundal part of the uterus, and is characterized as isthmical or type C contraction.

Although the number of type C contractions per minute did not decrease significantly from the mid- to the late-luteal phase in all groups of subjects, the mean frequency of type A contractions significantly ($P < 0.05$) decreased with the progression of the luteal phase, resembling recent data (Lesny *et al.*, 1998a,b; Fanchin *et al.*, 2001). This increasingly renders the fundal part of the uterus a region of relative peristaltic quiescence with the progression of the luteal phase. Since oestradiol stimulates type A contractile activities (Kunz *et al.*, 1998c), it seems reasonable to assume that progesterone constitutes the preliminary signal for the inhibition of fundal wave frequency during the luteal phase of the cycle (Ayoubi *et al.*, 2001). Progesterone has been shown to reduce myometrial contractility via genomic and non-genomic mechanisms (Graham and Clarke, 1997; Revelli *et al.*, 1998), while the application of the progesterone antagonist RU 486 stimulated uterine contractility during the luteal phase in the human (Gemzell-Danielsson *et al.*, 1993). Thus the pattern of luteal phase uterine peristalsis could be principally mimicked by the sequential exogenous administration of oestrogen and progesterone to hypogonadal women.

During the mid- as well as during the late-luteal phases, the progesterone serum concentrations in women following HMG administration were highly significantly increased as compared with the women with normal cycles and those hypogonadal women with solely exogenous steroid application. In contrast, not until the late secretory phase did the comparably high-elevated progesterone serum concentrations of those women administered HMG induce a significantly greater inhibition of type A peristaltic activity as compared with both the other groups of women. It might be assumed that a direct inhibition by systemic progesterone concentrations on type A peristaltic activity does not develop until the late-luteal phase presumably due to a delayed and cycle-dependant progesterone receptor formation and activation within the fundal myometrium. Furthermore, the influence of the utero-ovarian vascular countercurrent system on the control of fundal wave activity should also be emphasized (Einer-Jensen, 1988; Kunz *et al.*, 1998b). Sex steroids secreted from the fresh corpus luteum into the countercurrent vascular system were found in significantly higher concentrations in the upper third of the fundal myometrium as compared with the systemic concentrations (Einer-Jensen, 1988; Einer-Jensen *et al.*, 1989; Krzymowski, 1992). It seems conceivable that in women receiving HMG application (resulting in the development of multiple corpora lutea in both ovaries) the highly elevated secretion of progesterone into the

countercurrent vascular system as compared with normal cycles and cycles undergoing exogenous progesterone application significantly intensified the inhibition of type A peristalsis during the late-luteal phase. Vagina to uterus transport by progressive diffusion might also be used for the artificial control of uterine peristaltic activity (Bulletti *et al.*, 2001).

Type A as well as type C contractions start within the isthmical region, rendering this part of the uterus the prevailing pacemaker during the menstrual cycle. In the present study, the correlation coefficients between steroid hormone concentrations and the uterine peristaltic activities revealed controversial data for the different groups of subjects as well as for the phases of the menstrual cycle. However, recent studies have described oestrogens as the preliminary stimulator of isthmical pacemaker activity, with the induction of at least type A contractions (Rexroad, 1980; Kunz *et al.*, 1998c). Since the menstrual period concurs with low serum oestradiol concentrations, the activity of the isthmical pacemaker during the early phases of the menstrual cycle might be temporarily reduced and partly surpassed by alternative pacemakers of mainly fundal localization, which are probably governed by different endocrine signals confined to the menstrual period. Presumably, with the development of the dominant follicle the increasing oestradiol concentrations activate the pacemaker localized in the isthmical region of the womb, consequently rendering the isthmical region the prevailing pacemaker of at least type A myometrial contractions with the progression of the follicular phase. Because the serum oestradiol concentrations during the luteal phase still remain elevated as compared with the serum concentrations obtained during the menstrual period (**Table 1**), the isthmical region furthermore represents the dominant pacemaker region for the induction of type C and A uterine peristaltic contractions.

As during the pre-ovulatory period (Kunz *et al.*, 1998c), the isthmical pacemaker during the luteal phase is characterized by a refractoriness that cannot be surpassed even by the high serum concentrations of oestradiol observed in HMG cycles. Thus, type C wave frequency did not differ between the investigated groups. However, since in contrast to type A peristalsis type C contractions did not decrease significantly with the progression of the luteal phase, the activity of the isthmical pacemaker seems to be only marginally influenced by the serum concentrations of progesterone. However, as shown by the present study, progesterone-gaining access to the uterus either systemically or via the utero-ovarian countercurrent vascular system inhibits contractility and irritability of the fundal myometrium. As a consequence, with the progression of the luteal phase, contraction waves continually starting in the isthmical region cannot surpass the lower fundal myometrium due to the progesterone-induced refractoriness of the fundal myometrium.

Videosonography revealed that uterine peristaltic waves of the non-pregnant uterus are usually confined to the subendometrial myometrium or archimyometrium (De Vries *et al.*, 1990; Lyons *et al.*, 1991; Kunz *et al.*, 1996; Leyendecker *et al.*, 1996; Fanchin *et al.*, 2001; Van Gestel *et al.*, 2003). The archimyometrium, as the innermost of three myometrial layers, surrounds the whole endometrium and is characterized by a predominantly circular arrangement of the muscle fibres (Werth and Grusdew, 1898; Wetzstein, 1965; Noe *et al.*, 1999; Kunz *et al.*, 2000). Unlike the two outer layers of the myometrium that develop late during ontogeny and are therefore termed neomyometrium (Werth and Grusdew, 1898), the anlage of the archimyometrium can already be identified during the first trimester of gestation (hence its denomination). The ontogenetically early formation of the archimyometrium is pertinent to its function that results from the fusion of the two paramesonephric ducts and their mesenchymal elements to form the primordial uterus (Werth and Grusdew, 1898; Noe *et al.*, 1999). The bipartition of the circular subendometrial myometrium in the upper part of the uterine corpus and its separate continuation through the cornua into the respective tubes is the morphological basis of directed sperm transport into the tube ipsilateral to the dominant follicle (Kunz *et al.*, 1996, 1998b; Noe *et al.*, 1999). Thus directed passive transport of sperm (macrospheres) into the 'dominant' tube constitutes a genuine uterine function and results from both, the specific structure of the archimyometrium with its fundo-cornual bipartition of the circular fibres (Werth and Grusdew, 1898; Noe *et al.*, 1999) and the effects of the utero-ovarian counter-current system providing an ipsilaterally increased input of hormones from the dominant ovarian structure into the uterine cornual region (Kunz *et al.*, 1998b).

During the luteal phase, the archimyometrium is still active and directed, in that inert particles are preferentially transported into the tubes ipsilateral to the fresh corpus luteum. However, because the human embryo has a volume and weight many fold higher than the albumin macrospheres of sperm size used in HSSG, and due to the relative quiescence of the fundal myometrium with the progression of the luteal phase, it has to be assumed that uterine peristalsis during the secretory phases does not have the same capacity to transport an embryo into the isthmical parts of the tubes as it has to transport inert particles of sperm size (Kunz *et al.*, 1996; Leyendecker *et al.*, 1996). Nevertheless, the HSSG underlines that the principal directionality of the uterine peristaltic pump as observed during the mid- and late-follicular phases (Kunz *et al.*, 1996) is still preserved at least during the midluteal phase of the menstrual cycle.

In animal studies, beads of different sizes were used to examine the control of embryo implantation (Pope *et al.*, 1986). However, so far as is known, similar studies have never been performed in humans. The present study gained intriguing insights into the control of human embryo implantation provided by the uterine peristaltic pump.

About 4 days following ovulation, the human embryo enters the uterine cavity and remains for 2 days without implantation (Harper, 1994). During this time with no adhesive contact with the underlying endometrium, the uterus determines the final site of implantation, which is not random (Harper, 1994), and as observed in other mammals, appears to be species-specific (Lee *et al.*, 1977; Thorbert *et al.*, 1978; Stuckhardt *et al.*, 1981; Pope *et al.*, 1982a,b; Rogers *et al.*, 1983; Baird and Birney, 1985; Dziuk, 1985; Pope *et al.*, 1986; Rahima and Bruce, 1986; von Domarus *et al.*, 1986; Legrand *et al.*, 1987, 1989; Wiebold and Becker, 1987; Louton *et al.*, 1988; Nephew *et al.*, 1989, 1992; Tsutsui *et al.*, 2002). The present study revealed that in spontaneous singleton pregnancies, the gestational sacs were almost always located within the uterine horn ipsilateral to the site of the corpus luteum of pregnancy. These results correspond to previous observations (Kawakami *et al.*, 1993). This means that after entering the uterine cavity the human preimplantation

embryo usually does not migrate.

The clinical significance of ipsilateral implantation corresponds with the observation that in women suffering from missed abortions following spontaneous conceptions, significantly more embryos implanted centrally or contralateral to the site of the corpus luteum of pregnancy, and hence did migrate. On the one hand, it might be assumed that failure of luteal phase uterine peristalsis leads to contralateral implantation resulting in missed abortions. On the other hand, it has been shown that delayed implantation subsequent to ovulation and fertilization increased the risk of miscarriage in the human (Wilcox *et al.*, 1999). Since chromosomal anomalies have been described frequently in human embryos derived from missed abortions (Boue *et al.*, 1975; Rehder *et al.*, 1989) it seems conceivable that chromosomal aberrations in the blastocyst delay implantation and thus increase the rate of migration and consequently the probability of central or contralateral implantation.

Furthermore, there is compelling evidence that the decrease of type A contraction waves with the progression of the luteal phase protects the embryo from tubal regurgitation. However, preliminary data have shown that presumably due to a dysfunction of the uterine peristaltic pump transuterine migration of the primarily intrauterine arrived blastocyst into the tube contralateral to the site of the corpus luteum might contribute to the aetiology of tubal pregnancy in spontaneous conception cycles (Kunz and Leyendecker, unpublished). On the other hand, it has to be assumed that the few type A contractions also protect the embryo from implantation within lower uterine regions, which would result in placenta praevia.

However, the corpus luteum controls the site of ipsilateral embryo implantation in the same way as the dominant follicle directs sperm transport into the ipsilateral tube (Kunz *et al.*, 1996, 1997, 1998b). The fact that following fresh IVF–embryo transport, the embryos again usually do not migrate but do so following cryopreservation cycles, demonstrates the influence of the corpus luteum via the utero-ovarian vascular countercurrent system (Einer-Jensen, 1988; Kunz *et al.*, 1998b) on the directional activity of the archimyometrium providing embryo migration and implantation. In cryopreservation cycles, no direct access of endocrine signals from the ovary to the uterus could cause a gradient of signal expression within the fundal myometrium and thus be responsible for directed uterine functions such as providing ipsilateral high fundal embryo implantation. As a consequence, the preimplantation embryo following embryo transport in cryopreservation cycles migrates more frequently than following fresh IVF–embryo transport with multiple corpora lutea in both ovaries providing endocrine signals towards each ipsilateral uterine horn. How far increased embryo migration in assisted reproduction cycles influences the rates of conceptions remains to be further elucidated. Other studies did not show any correlation between the frequency of mid- and late-luteal phase peristalsis following IVF–embryo transfer and the pregnancy rates as emphasized by others (Fanchin *et al.*, 1998, 2001; Lesny *et al.*, 1998; Ayoubi *et al.*, 2003; Kunz and Leyendecker, unpublished). Implantation rates following IVF are also influenced by the type of transfer catheters (Abou-Setta *et al.*, 2006).

HSSG has further shown that cervical mucus during the luteal phase does not act as a barrier against the transport of inert particles, corresponding to a recent study which has shown spermatozoa to be present in the uterine cavity following vaginal insemination during the luteal phase (Faundes *et al.*, 1981). Therefore, bacteria may be aspirated from the vagina into the uterine cavity, especially during intercourse, by the peristaltic pump. Thus, a strong antibacterial defence system must exist within the upper genital tract in addition to the vaginal defence system involving vaginal lactobacilli. MUC1 is expressed within the uterine and tubal epithelium (Gipson *et al.*, 1997) and, following ovulation, there is an influx of bone marrow-derived white cells into the endometrium (Loke and King, 1996; Herbertz, Kunz and Leyendecker, unpublished). The latter is primarily viewed to be involved in the immunological control of implantation. In view of the present results and of those reported in the literature, it may be regarded as a phylogenetically old antibacterial defence system that in placental species was modified during the phylogeny of the reproductive system in order to control the invasion of the endometrium by the trophoblast (Hunt and Robertson, 1996; Barrat and Pockley, 1998).

It has been demonstrated that women suffering from endometriosis developed uterine hyper- and dysperistalsis throughout the menstrual cycle (Leyendecker *et al.*, 1996). With respect to the analysis of uterine contractility as performed in the present study, differentiating into three types of contraction waves (A, B and C) the VSUP records of those women published (Leyendecker *et al.*, 1996) were reviewed. The reanalysis of uterine peristalsis confirmed previously obtained data (Leyendecker *et al.*, 1996). Uterine hyper- and dysperistalsis is a common finding in women suffering from endometriosis and sterility, which could be observed throughout the menstrual cycle. Endometriosis constitutes a disease of the archimetra and has been described recently in great detail (Leyendecker *et al.*, 1996, 1998, 2006; Kunz *et al.*, 2000, 2005).

In conclusion, this study provides insights into the function and control of uterine peristaltic activity during the luteal phase of the menstrual cycle. The uterine peristaltic pump is significantly active during the luteal phase of the cycle as shown by HSSG in order to sustain embryo implantation within the uterine horn. Presumably, progesterone secretion from the fresh corpus luteum systemically and into the utero-ovarian vascular countercurrent system renders the fundo-cornual region a zone of relative peristaltic quiescence with the progression of the luteal phase thus minimizing mechanical irritation of the process of implantation and early embryonal growth. However, the data indicate that fundo-cornual implantation on the side of the dominant structure as provided by early and midluteal phase uterine peristalsis might be fundamental with respect to a successful pregnancy. Hormone secretion from the fresh corpus luteum into the utero-ovarian vascular countercurrent system constitutes the preliminary mechanism providing ipsilateral high fundal embryo implantation. Increased migration of the preimplantation embryo might result in early pregnancy loss. Furthermore, luteal phase cervical mucus does not act as a barrier against the ascension of spermatozoa and alternative kind of debris such as bacteria; hence an anti-inflammatory defence system appears to be crucial. There is evidence that the antibacterial defence system in placentalian species was modified during the phylogeny of the reproductive system in order to control the invasion of the endometrium by the trophoblast.

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