Human Reproduction Update 1998, Vol. 4, No. 5 pp. 647–654

Uterine peristalsis during the follicular phase of the menstrual cycle: effects of oestrogen, antioestrogen and oxytocin

G.Kunz[1], M.Noe[1], M.Herbertz[2] and G.Leyendecker[1,3]

Departments of [1]Obstetrics and Gynaecology and [2]Pathology, Klinikum Darmstadt, Academic Teaching Hospital to the University of Frankfurt, Darmstadt, Germany

TABLE OF CONTENTS

Uterine peristalsis, directing sustained and rapid sperm transport from the external cervical os or the cervical crypts to the isthmic part of the tube ipsilateral to the dominant follicle, changes in direction and frequency during the menstrual cycle, with lowest activity during menstruation and highest activity at mid cycle. It was therefore suggested that uterine peristalsis is under the control of the dominant follicle with the additional involvement of oxytocin. To test this hypothesis, vaginal sonography of uterine peristalsis was performed in the early, mid and late proliferative phases, respectively, of cycles of women treated with oestradiol valerate and with human menopausal gonadotrophin following pituitary downregulation, with clomiphene citrate and with intravenous oxytocin, respectively. Administration of oestradiol valerate resulted in oestradiol serum concentrations comparable with the normal cycle with a simulation of the normal frequency of peristaltic contractions. Elevated oestradiol concentrations and bolus injections of oxytocin resulted in a significant increase in the frequency of peristaltic contractions in the early and mid follicular phases, respectively. Chlomiphene tended, though insignificantly so, to suppress the frequency of peristaltic waves in the presence of elevated oestradiol concentrations. In the late follicular phase of the cycle extremely elevated oestradiol concentrations as well as the injection of oxytocin resulted only in an insignificant further increase of peristaltic frequency. In the normal cycles, as well as during extremely elevated oestradiol concentrations and following oxytocin administration, the peristaltic contractions were always confined to the subendometrial layer of the muscular wall. The results and the review of literature indicate that uterine peristalsis during the follicular phase of the menstrual cycle is controlled by oestradiol released from the dominant follicle with the probable involvement of oxytocin, which is presumably stimulated together with its receptor within the endometrial–subendometrial unit and therefore acting in an autocrine/paracrine fashion. Since unphysiological stimulation with oestradiol and oxytocin did not significantly increase the frequency of uterine peristalsis in the late follicular phase of the cycle it is assumed that normal preovulatory frequency of uterine peristalsis is at a level which cannot be significantly surpassed due to phenomena of refractoriness of the system.

Key words: oestrogen/oxytocin/sperm transport/uterine peristalsis

Introduction

Passive sperm transport through the female genital tract is under the endocrine control of the dominant follicle not only with respect to the level to which spermatozoa are transported, but also with regard to the direction in which such transport occurs (Kunz *et al.*, 1996, 1997). Oxytocin and prostaglandins most likely act as mediators in this system of coordinated uterine contractions (Eliasson and

[3]To whom correspondence should be addressed

Posse, 1960; Hein *et al*., 1973; Karim and Hillier, 1973; Fuchs *et al*., 1985; Takemura *et al*., 1993; Lefebvre *et al*., 1994a,b; Zingg *et al*., 1995). Furthermore, the specific architecture of the myometrium plays a significant role in this regard (Werth and Grusdew, 1898; Wetzstein, 1965; Noe *et al*., 1998). However, the exact mechanisms that govern this system of directed rapid sperm transport remain to be elucidated.

In this study, we examined the effects of exogenous administration of oestrogen and antioestrogen, of supraphysiologically increased concentrations of oestradiol during cycles of ovarian hyperstimulation, and of oxytocin on the peristaltic activity of the uterus during the proliferative phase of the cycle.

Assessment of uterine peristalsis

Patients and volunteers

A total of 108 women (mean age 30 years; range 22–46 years) entered this study after providing their informed consent.

Study design

Study 1: Thirteen women received daily, orally administered oestradiol valerate (Progynova®; Schering AG, Berlin, Germany) following pituitary downregulation with triptorelin (Decapeptyl-Depot®; Ferring Arzneimittel GmbH, Kiel, Germany) treatment during the mid-luteal phase of the preceding cycle. Oestradiol valerate was administered at doses of 4 mg for days 1–3, 6 mg for days 4–9, and 8 mg for days 10–15 in order to prepare the endometrium for embryo transfer following cryopreservation of pronuclear (PN) state oocytes. Vaginal sonography of uterine peristalsis (VSUP) was performed on days 2–4, 7–9 and 12–13, respectively.

Study 2: Ten women received 100 mg of clomiphene citrate (Dyneric®; Marion Merrel Dow GmbH, Rüsselsheim, Germany) on days 5–9 of the cycle. Clomiphene citrate was administered to stimulate the ovaries and endometrium for embryo transfer following cryopreservation of PN state oocytes. VSUP was performed on days 5–7, 10–13 and on day 15 of the cycle, respectively.

Study 3: Twenty women received supraphysiological quantities of endogenous oestradiol in cycles of ovarian hyperstimulation for artificial reproductive technology. The women were treated with human menopausal gonadotrophins (HMG) (Menogon®; Ferring Arzneimittel GmbH, Kiel, Germany) at mean daily doses of 225 IU of follicle stimulating hormone (FSH) and 225 IU of luteinizing hormone (LH), respectively, following pituitary downregulation with triptorelin (Decapeptyl-Depot®; Ferring Arzneimittel GmbH) according to the long protocol (Leyendecker *et al*., 1990). VSUP was performed on days –5, –3 and –1 of human chorionic gonadotrophin (HCG) administration, respectively.

A group of women (n = 46) whose uterine peristaltic activity during the follicular phase of the cycle had been documented previously (Leyendecker *et al*., 1996) served as controls for studies 1–3.

Study 4: Nineteen women received 3 IU of oxytocin (Syntocinon®; Sandoz AG, Nürnberg, Germany) as an i.v. bolus in the early follicular phase (n = 4), mid follicular (n = 9) and late follicular phases (n = 6), respectively, of normal menstrual cycles. VSUP was performed during 5-min periods immediately before and after oxytocin administration. Thus, the women in the oxytocin study served as their own controls.

On the days of VSUP, blood samples were obtained for the determination of the respective serum oestradiol concentrations.

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 provide a sagittal section of the whole uterus and was maintained in a fixed position over a period of 5 min. The whole scan was videotaped for quantitative assessment of uterine peristalsis, the tape being replayed at 5× regular speed in order to estimate precisely the frequency of the contraction waves. This also facilitated determination of the wave direction (cervicofundal versus fundocervical peristalsis).

Hormone measurements

Oestradiol-17β concentrations in serum were measured using a commercially available enzyme immunoassay system.

Statistical analysis

Statistical analysis was performed with Student's *t*-test.

Effects of ovarian stimulation and oxytocin on uterine peristalsis

The results of the studies are presented in Figures 1–4 and Tables I–IV, respectively. Follicular diameters and serum oestradiol concentrations, as well as the frequency of the uterine peristalsis, during the early, mid and late follicular phase of the control cycles are shown in Table V.

Study 1: Oestradiol valerate administration resulted in oestradiol serum concentrations similar to those of the normal proliferative phase of the menstrual cycle (Figure

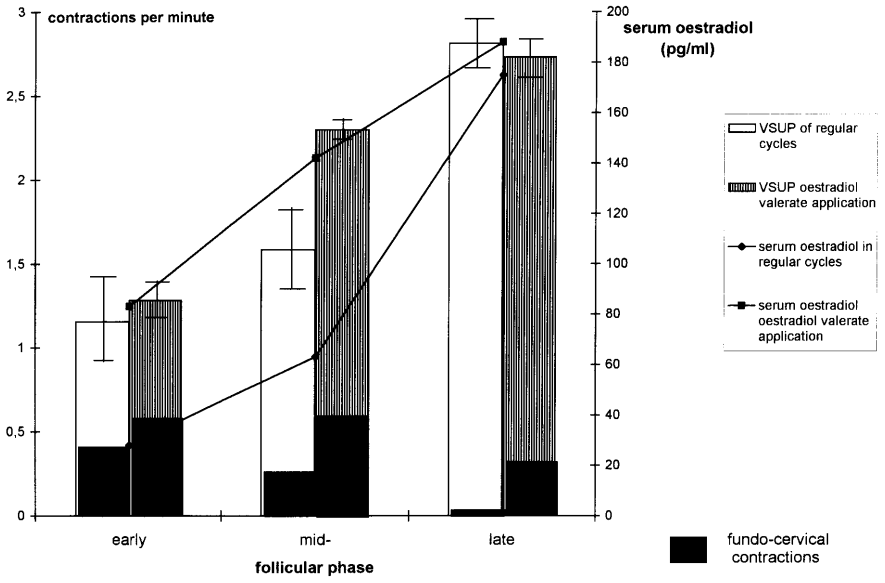

Figure 1. Graphical demonstration of the frequency of the subendometrial uterine peristaltic waves during the early, mid and late follicular phases, as determined by vaginal ultrasonography (mean ± SEM contractions/min) during the normal menstrual cycle and in women receiving an daily oral dose of oestradiol valerate following downregulation with a GnRH analogue. The relative distribution of fundocervical versus cervicofundal contractions during these different phases of the cycle is also shown.

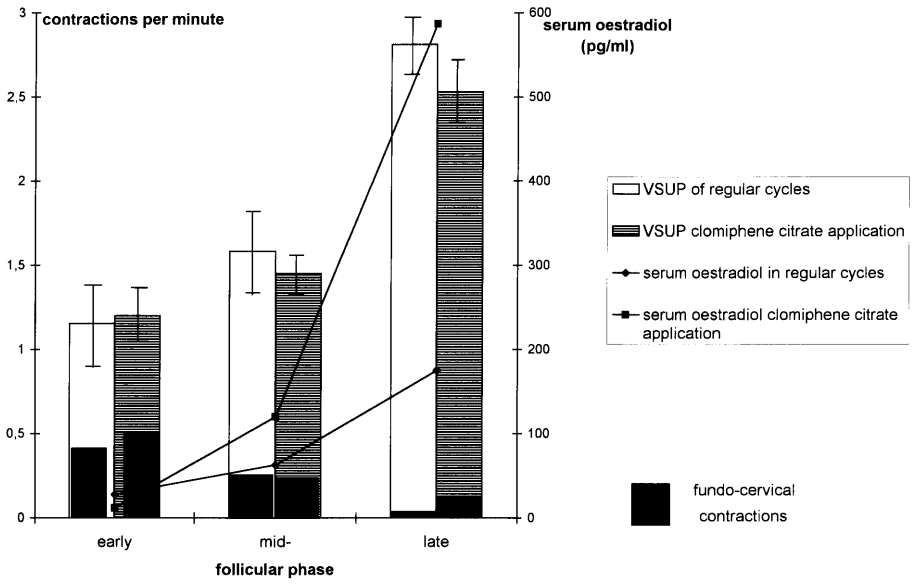

Figure 2. Graphical demonstration of the frequency of the subendometrial uterine peristaltic waves during the early, mid and late follicular phases, as determined by vaginal ultrasonography (mean ± SEM contractions/min) during the normal menstrual cycle and in women receiving daily oral doses of 100 mg clomiphene citrate from days 5–9. The relative distribution of fundocervical versus cervicofundal contractions during these different phases of the cycle is also shown.

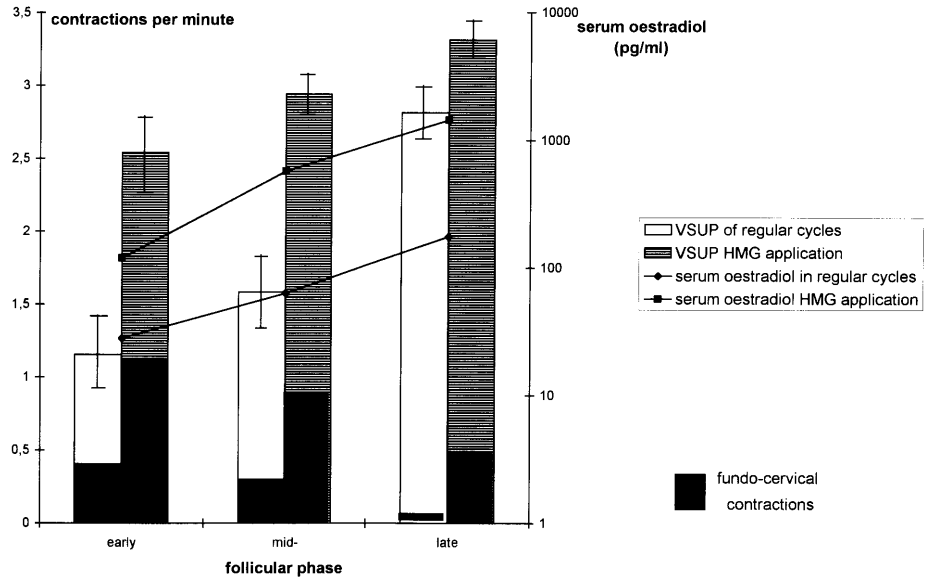

Figure 3. Graphical demonstration of the frequency of the subendometrial uterine peristaltic waves during the early, mid and late follicular phases, as determined by vaginal ultrasonography (mean ± SEM contractions/min) during the normal menstrual cycle and in women treated with human menopausal gonadotrophin (HMG) for ovarian superovulation. The findings in the normal cycles and in the treatment cycles were correlated on the basis of the sizes of the dominant and leading dominant follicle, respectively. The relative distribution of fundocervical versus cervicofundal contractions during these different phases of the cycle is also shown.

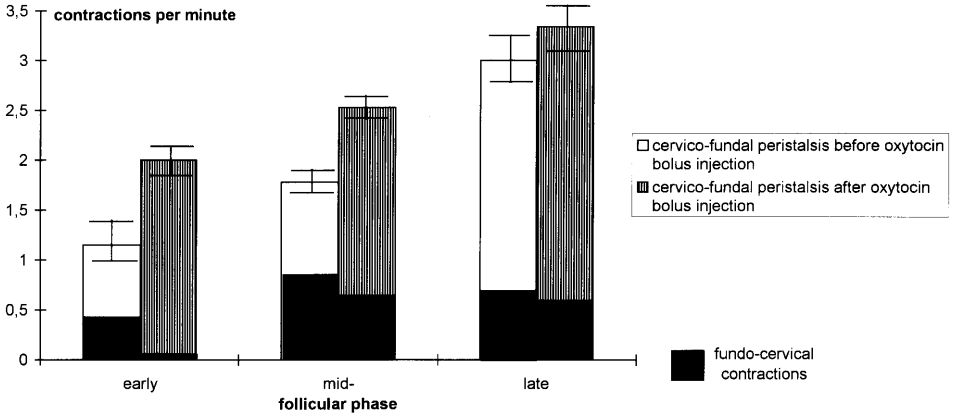

Figure 4. Graphical demonstration of the frequency of the subendometrial uterine peristaltic waves during the early, mid and late follicular phases, as determined by vaginal ultrasonography (mean ± SEM contractions/min) during the normal menstrual cycle before and immediately after an i.v. bolus injection of 3 IU of oxytocin. Injection of normal saline alone had no effect (not shown). The relative distribution of fundocervical versus cervicofundal contractions during these different phases of the cycle is also shown.

1; Table I). The frequency of peristaltic waves during oestradiol treatment increased in parallel with that of normal cycles. At days 7–9 of treatment, serum oestradiol concentrations were significantly higher than those of the normal mid follicular phase, but only at this stage did the frequency of peristaltic waves significantly surpass those of normal cycles.

Table I. The diameter of the dominant follicle and serum concentrations of oestradiol and progesterone during the early, mid and late follicular phase in patients with vaginal sonography of uterine peristalsis during oestradiol valerate treatment. Values are means ± SD.

Phase of cycle	n	Follicular diameter (mm)	Serum oestradiol (pg/ml)	Serum progesterone (ng/ml)
Early follicular	13	–	83 ± 37	0.3 ± 0.3
Mid follicular	13	–	142 ± 59	0.4 ± 0.35
Late follicular	13	–	229 ± 188	0.3 ± 0.25

Table II. The diameter of the dominant follicle and serum concentrations of oestradiol and progesterone during the early, mid and late follicular phase in patients with vaginal sonography of uterine peristalsis during clomiphene citrate treatment. Values are means ± SD.

Phase of cycle	n	Follicular diameter (mm)	Serum oestradiol (pg/ml)	Serum progesterone (ng/ml)
Early follicular	10	< 10	12 ± 7	0.4 ± 0.4
Mid-follicular	10	13 ± 0.7	179 ± 110	0.5 ± 0.3
Late follicular	10	20 ± 1.4	567 ± 364	0.6 ± 0.5

Table III. The diameter of the dominant follicle and serum concentrations of oestradiol and progesterone during the early, mid and late follicular phase in patients with vaginal sonography of uterine peristalsis during gonadotrophin treatment. Values are means ± SD.

Phase of cycle	n	Follicular diameter (mm)	Serum oestradiol (pg/ml)	Serum progesterone (ng/ml)
Early follicular	20	< 11	119 ± 43	Not measured
Mid follicular	20	13 ± 1.2	571 ± 485	Not measured
Late follicular	20	19 ± 1.8	1435 ± 1156	Not measured

Table IV. The diameter of the dominant follicle and serum concentrations of oestradiol and progesterone during the early, mid and late follicular phase in patients with vaginal sonography of uterine peristalsis during a bolus injection of oxytocin. Values are means ± SD.

Phase of cycle	*n*	Follicular diameter (mm)	Serum oestradiol (pg/ml)	Serum progesterone (ng/ml)
Early follicular	4	< 10	39 ± 28	0.8 ± 0.5
Mid follicular	9	14 ± 3.4	89 ± 76	0.3 ± 0.2
Late follicular	6	19 ± 0.8	142 ± 114	2.6 ± 2.2

Table V. The diameter of the dominant follicle and serum concentrations of oestradiol and progesterone during the early, mid and late follicular phase of the normal cycle in healthy patients. Values are means ± SD.

Phase of cycle	*n*	Follicular diameter (mm)	Serum oestradiol (pg/ml)	Serum progesterone (ng/ml)
Early follicular	14	<11	28 ± 13	0.5 ± 0.5
Mid follicular	22	14 ± 1.6	63 ± 31	0.4 ± 0.3
Late follicular	10	18 ± 1.4	175 ± 107	0.9 ± 1.09

Study 2: Stimulation of ovarian function with clomiphene citrate led to a supraphysiological increase in serum oestradiol concentrations which were significantly higher than those of the normal cycle and approximately 3-fold those in the late follicular phase (Figure 2; Table II). Peristaltic frequencies of normal cycles and following clomiphene citrate treatment were not significantly different. It was noted, however, that in the face of significantly increased oestradiol concentrations in the late follicular phase, peristaltic frequency tended to be lower in clomiphene citrate cycles as compared with normal cycles.

Study 3: Stimulation of ovarian function with HMG in an in-vitro fertilization (IVF) protocol resulted in supraphysiological concentrations of serum oestradiol (Table III) that differed significantly from those of normal cycles, as they were compared on the basis of the diameters of the dominant (in normal cycles) and leading (in stimulated cycles) follicles, respectively. The respective frequencies of peristaltic contractions differed significantly between normal and HMG-stimulated cycles during the early and mid follicular phases, but not (P = 0.06) during the late follicular phases.

Study 4: In healthy women with normal menstrual cycles, an i.v. bolus of 3 IU of oxytocin resulted in an abrupt and significant increase in the frequency of the peristaltic contractions during both the early and mid follicular phases of the cycle. The increment in frequency of contractions in the late follicular phase was not significant (Figure 4; Table IV). It should be noted that, in the uterine peristaltic activity that increased following an oxytocin bolus, only the subendometrial myometrium was involved. Bolus injections of placebo had no effect (data not shown).

In the early and mid follicular phases of the cycle, supraphysiological serum concentrations of oestradiol or the administration of oxytocin resulted in significant increases in the frequency of uterine peristaltic contractions. However, this increase was not significant in the late follicular phase, the mean frequency being similar (3.3 contractions/min) after either treatment (Figures 3 and 4).

Activity and regulation of uterine peristaltic activity

Uterine peristaltic activity increases with the progression of the follicular phase (Lyons *et al*., 1991; Kunz *et al*., 1996; Leyendecker *et al*., 1996). In women rendered hypogonadal following the administration of a long-acting gonadotrophin releasing hormone (GnRH) analogue the administration of oestradiol valerate—in simulating the increase of oestradiol in blood during the follicular phase of the cycle—resulted in a pattern of uterine peristalsis that was similar to that of the normal follicular phase (Figure 1). While the administration of an antioestrogen appeared to attenuate the effects of oestradiol on uterine peristalsis (Figure 2), peristaltic activity was dramatically increased by unphysiologically elevated oestradiol concentrations during HMG administration (Figure 3). Thus, the data presented clearly indicate that uterine peristalsis during the follicular phase of the menstrual cycle is controlled by oestradiol secreted from the dominant follicle.

Uterine peristaltic activity only involves the stratum subvasculare of the myometrium and not the other layers, the stratum vasculare and supravasculare (Birnholz, 1984; De Vries *et al*., 1990; Lyons *et al.*, 1991; Kunz *et al*., 1996). In contrast to those two outer layers (Noe *et al*., 1999), the stratum subvasculare shows a cyclic pattern of oestradiol receptor expression in that low levels are found during the early follicular and late luteal phases and high levels at mid cycle (Lessey *et al*., 1988; Snijders *et al*., 1992; Noe *et al*., 1999). It is therefore reasonable to assume that the cyclic activity of uterine peristalsis is functionally related to the cyclically changing oestradiol receptor expression, as well as to the changing oestradiol concentrations in blood.

The stimulatory action of oestradiol on uterine contractility, however, is probably indirect and involves a cascade of transcriptional events such as induced synthesis of growth factors, enzymes, local hormones and receptors, such as those for oxytocin (Katzenellenbogen *et al*., 1979; Cole and Garfield, 1989; Soloff, 1989; Batra, 1994; Zingg *et al*., 1995). Our study demonstrates that oxytocin is able to increase significantly the frequency of the peristaltic contractions (Figure 4). As the spontaneous contractile waves, those enhanced by exogenous oxytocin are confined to the stratum subvasculare of the myometrium and do not involve the other myometrial layers.

It has been shown recently in rodents that oxytocin is produced in large amounts in the endometrium and that endometrial oxytocin (OT) and oxytocin receptor (OTR) mRNA expression is highest at oestrous and is upregulated by oestradiol (Zingg *et al*., 1995). A quantitative analysis of the production of oxytocin within the hypothalamus and in the endometrium favours the view that oxytocin, being functionally effective in the uterus, is produced locally rather than in the central nervous system (Zingg *et al*., 1995).

However, ovarian oxytocin might also play a role in the control of uterine peristalsis, at least at mid cycle, in addition to assumed ovarian paracrine effects (Einspanier *et al.*, 1995; Furuya *et al*., 1995). Synthesis and release of follicular oxytocin is sharply increased following the onset of the LH surge or the administration of HCG (Schaeffer *et al*., 1984; Ivell *et al*., 1985; Tjugum *et al*., 1986; Peek *et al*., 1987; Fortune and Voss, 1993). In hysterosalpingoscintigraphy (Kunz *et al*., 1996), following the administration of oxytocin in the mid-follicular phase of the cycle, the ascent of inert particles within the uterine tract is dramatically enhanced (Wildt *et al*., 1998). Thus, follicular oxytocin could further stimulate directed sperm transport around the time of ovulation. The increase in frequency of peristaltic waves at mid cycle, however, was not significant following the injection of oxytocin (Figure 4). It appears that, at mid cycle, spontaneous uterine peristaltic frequency has reached a level which cannot be surpassed significantly by unphysiological stimulation, probably due to phenomena such as refractoriness of the system (Figures 3 and 4).

OTR have been shown to be present in the human non-pregnant uterus at a significantly lower concentration in comparison with the pregnant uterus at parturition (Fuchs *et al*., 1985; Soloff, 1989). During the cycle, OTR concentrations (monitored by binding assays) were lowest at mid cycle and highest at the end of the luteal phase and during menstruation (Maggi *et al*., 1992). Using immunocytochemistry of OTR, similar results were obtained during the cycle in marmoset monkeys (Einspanier *et al*., 1998) and human myometrium (Fuchs *et al*., 1998). With regard to the longitudinal distribution of OTR in the human non-pregnant uterus, highest concentrations were found in the fundal region of the uterus and intermediate concentrations in the isthmic region (Fuchs *et al*., 1985). With respect to the myometrial layers, autoradiographical localization of oxytocin binding sites in the myometrium could be demonstrated only in the outer longitudinal smooth muscle layer in the ovine oestrous cycle (Wallace *et al*., 1991). In the marmoset monkey, there was a small increase in OTR expression during mid cycle and a trend to a higher concentration in the inner part of the myometrium (Einspanier *et al*., 1998).

With respect to human endometrium, OTR expression could be demonstrated in endometrial epithelium with highest values around ovulation, but not in the endometrial stroma (Takemura *et al*., 1993); this corresponded to data obtained in the cycle of marmoset monkeys (Einspanier *et*

al., 1998). In rodents, endometrial mRNA for the OTR is highest during oestrus as well as during pregnancy and is upregulated by exogenous oestradiol and synergistically by progesterone (Lefebvre *et al*., 1994a,b; Zingg *et al*., 1995). The demonstration of OTR expression and that of the ligand in the same tissue and even in the same cell was interpreted as there being an autocrine/paracrine system within the endometrium (Takemura *et al*., 1993; Zingg *et al*., 1995).

A functional effect of the endometrial oxytocin/OTR autocrine/paracrine system on the subendometrial myometrium would involve mediators of oxytocin action such as the prostaglandins. Uterine contractions elicited by oxytocin, at least in pregnancy, are believed to be linked with prostaglandin release (Soloff and Hinko, 1993; Fuchs *et al*., 1996b; Chaud *et al*., 1997a). Prostaglandin $F_{2\alpha}$ was shown to be increased in the myometrium of various pregnant animals near term relative to the increase of OTR (Soloff and Hinko, 1993; Fuchs *et al*., 1996a) and their concentration determines the magnitude of oxytocin-induced prostaglandin $F_{2\alpha}$ release. In addition, nitric oxide synthase (NOS) has been identified in the human myometrium and the glandular epithelium, but not in the stroma of the endometrium (Telfer *et al*., 1995, 1997), which suggests that nitric oxide may play a role in endometrial and myometrial function. In the pregnant rat, NOS activity was stimulated by oxytocin and nitric oxide and can regulate oxytocin/prostaglandin $F_{2\alpha}$-induced contractions as well as prostaglandin synthesis (Chaud *et al*., 1997b). In the oestrogenized rat, however, neither nitric oxide nor prostaglandins are involved in uterine contractions induced by oxytocin (Chaud *et al*., 1997a). In our own studies, a rectal dose of 50 mg of indomethacin, which usually blocks premature contractions in pregnancy for about 4 h, was ineffective in reducing the frequency of peristaltic contractions during the mid-follicular phase of the cycle (unpublished results). Zingg *et al*. (1995) suggested that endometrial oxytocin may pass the thin layer of stroma existing between the tip of the uterine glands and the myometrium, and interact directly with myometrial OTR. This view, however, makes it mandatory to re-examine the controversial results on OTR expression in the subendometrial myometrium during oestrous and the menstrual cycle.

The directionality of uterine peristalsis with predominantly cervicofundal waves of contraction emerging in the isthmic region of the uterus is a striking phenomenon, which may be related to the finding of a high concentration of OTR in the bovine cervical mucosa at oestrus (Fuchs *et al*., 1996b), thus rendering the cervix as the possible pacemaker of cervicofundal contractions. In oestrous ewes, oxytocin binding site concentrations were highest within the inner dense collagenous cervix in comparison with pregnant, ovariectomized or anoestrous animals (Matthews and Ayad, 1994). Since oxytocin was found to stimulate prostaglandin E_2 output *in vitro* in bovine cervical tissue and since prostaglandin E_2 is capable of softening cervical tissue (Fuchs *et al*., 1996b), the preovulatory softening of the cervix and widening of the external cervical os in women may be an action of oxytocin mediated by prostaglandin E_2. With respect to sperm transport, the softening of the cervical tissue allows the cervix to be compressed at the moment of the initiation of a peristaltic wave in the cervicoisthmic region of the uterus. Spermatozoa are thus squeezed out of the cervical crypts and the preovulatorily abundant mucus protrudes from the cervix. This enlarges the contact zone between the mucus and a fresh ejaculate and optimizes sperm transport from the vaginal depot as well as from the primary reservoir within the cervical crypts to the isthmic part of the tube ipsilateral to the dominant follicle (Kunz *et al*., 1996, 1997).

References

Batra, S. (1994) Hormonal control of myometrial function. In Chard, T. and Grudzinskas, J.G. (eds), *The Uterus*. Cambridge Reviews on Human Reproduction, pp. 173–192.

Birnholz, J. (1984) Ultrasonic visualization of endometrial movements. *Fertil. Steril*., **41**, 157–158.

Chaud, M., Franchi, A.M., Rettori, V. *et al*. (1997a) Nitric oxide in the contractile action of bradykinin, oxytocin, and prostaglandin F2 alpha in the estrogenized rat uterus. *Proc. Natl Acad. Sci. USA*, **94**, 11049–11054.

Chaud, M.A., Franchi, A.M., Beron de Astrada, M. and Gimeno, M.F. (1997b) Role of nitric oxide on oxytocin evoked contractions and prostaglandin synthesis in isolated pregnant rat uterus. *Prostaglandins Leukot. Essent. Fatty Acids*, **57**, 323–329.

Cole, W.C. and Garfield, R.E. (1989) Ultrastructure of the myometrium. In Wynn, R.M. and Jollie, W.P. (eds), *Biology of the Uterus*. Second edition. Plenum Medical Book Co., New York, pp. 455–504.

De Vries, K., Lyons, E.A., Ballard, G. *et al*. (1990) Contractions of the inner third of the myometrium. *Am. J. Obstet. Gynecol*., **162**, 679–682.

Einspanier, A., Ivell, R. and Hodges, J.K. (1995) Oxytocin: a follicular luteinsation factor in the marmoset monkey. *Adv. Exp. Med. Biol*., **395**, 517–522.

Einspanier, A., Bielefeld, A. and Kopp, J.-H. (1998) Expression of the oxytocin receptor in relation to steroid receptors in the uterus of a primate model, the marmoset monkey. *Hum. Reprod Update*, **4**, 634–646.

Eliasson, R. and Posse, N. (1960) The effect of prostaglandin on the nonpregnant uterus *in vivo*. *Acta Obstet. Gynecol. Scand*., **39**, 112.

Fortune, J.E. and Voss, A.K. (1993) Oxytocin gene expression and action in bovine preovulatory follicles. *Regul. Pept*., **45**, 257–261.

Fuchs, A.R., Fuchs, F. and Soloff, M.S. (1985) Oxytocin receptors in nonpregnant human uterus. *J. Clin. Endocrinol. Metab*., **60**, 37–41.

Fuchs, A.R., Ivell, R., Fields, P.A. *et al*. (1996a) Oxytocin receptors in the bovine cervix: distribution and gene expression during the estrous cycle. *Biol. Reprod*., **54**, 700–708.

Fuchs, A.R., Rollyson, M.K., Meyer, M. *et al*. (1996b) Oxytocin induces prostaglandin F2alpha release in pregnant cows: influence of

gestational age and oxytocin receptor concentrations. *Biol. Reprod*., **54**, 647–653.

Fuchs, A.R., Behrens, O., Maschek, H. *et al*. (1998) Oxytocin and vasopressin receptors in human and uterine myomas during menstrual cycle and early pregnancy. *Hum. Reprod. Update*, **4,** 594–604.

Furuya, K., Mizumoto, Y., Makimura, N. *et al*. (1995) A novel biological aspect of ovarian oxytocin: gene expression of oxytocin and oxytocin receptor in cumulus/luteal cells and the effect of oxytocin on embryogenesis in fertilized oocytes. *Adv. Exp. Med. Biol*., **395**, 532–528.

Garfield, R.E. and Yallampalli, C. (1994) Structure and function of uterine muscle. In Chard, T. and Grudzinskas, J.G. (eds), *The Uterus*. Cambridge Reviews on Human Reproduction. pp. 54–93.

Hein, P.R., Eskes, T.K.A.B., Stolte, L.A.M. *et al*. (1973) The influence of steroids on uterine motility in the nonpregnant human uterus. In Josimovich, J.B. (ed.), *Uterine Contractions – Side Effect of Steroidal Contraceptives*. Wiley & Sons, New York, pp. 107–140.

Ivell, R., Brackett, K.H., Fields, M.J. and Richter, D. (1985) Ovulation triggers oxytocin gene expression in the bovine ovary. *FEBS Lett*., **190**, 263–267.

Karim, S.M.M. and Hillier, K. (1973) The role of prostaglandins in myometrial contraction. In Josimovich, J.B. (ed.), *Uterine Contractions – The Effects of Steroidal Contraceptives*. Wiley & Sons, New York, pp. 141–169.

Katzenellenbogen, B.S., Bhakoo, H.S., Ferguson, E.R. *et al*. (1979) Estrogen and antiestrogen action in reproductive tissues and tumors. *Rec. Prog. Hormone Res*., **35**, 292–300.

Kunz, G., Beil, D., Deininger, H. *et al*. (1996) The dynamics of rapid sperm transport through the female genital tract. Evidence from vaginal sonography of uterine peristalsis (VSUP) and hysterosalpingoscintigraphy (HSSG). *Hum. Reprod*., **11**, 627–632.

Kunz, G., Beil, D., Deininger, H. *et al*. (1997) The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. *Adv. Exp. Med. Biol*., **424**, 267–277.

Lefebvre, D.L., Farookhi, R., Giaid, A. *et al*. (1994a) Uterine oxytocin gene expression. II. Induction by exogenous steroid administration. *Endocrinology*, **134**, 2562–2566.

Lefebvre, D.L., Farookhi, R., Larcher, A. *et al*. (1994b) Uterine oxytocin gene expression. I. Induction during pseudopregnancy and the estrous cycle. *Endocrinology*, **134**, 2556–2561.

Lessey, B.A., Killiam, A.S.P., Metzger, D.A. *et al*. (1988) Immunohistochemical analysis of human uterine estrogen and progesterone receptors throughout the menstrual cycle. *J. Clin. Endocrinol. Metab*., **67**, 334–340.

Leyendecker, G., Bernart, W., Bremen, Th. *et al*. (1990) Influence of the duration of the oestradiol rise on the success rate in GnRH analogue/HMG stimulated IVF cycles. *Hum. Reprod*., **5**. 52–55.

Leyendecker, G., Kunz, G., Wildt, L. *et al*. (1996) Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. *Hum. Reprod*., **11**, 1542–1551.

Lyons, E.A., Taylor, P.J., Zheng, X.H. *et al*. (1991) Characterization of subendometrial myometrial contractions throughout the menstrual cycle in normal fertile women. *Fertil. Steril*., **55**, 771–775.

Maggi, M., Magini, A., Fiscella, A. *et al*. (1992) Sex steroid modulation of neurohypophysial hormone receptors in human nonpregnant myometrium. *J. Clin. Endocrinol. Metab*., **74**, 385–392.

Matthews, E.L. and Ayad, V.J. (1994) Characterization and localization of a putative oxytocin receptor in the cervix of the oestrous ewe. *J. Endocrinol*., **142**, 397–405.

Noe, M., Kunz, G., Herbertz, M. *et al*. (1999) The cyclic pattern of the immunocytochemical expression of oestrogen and progesterone receptors in human myometrial and endometrial layers: characterisation of the endometrial–subendometrial unit. *Hum. Reprod*., **14**, in press.

Peek, J.C., Choy, V.J., Watkins, W.B. and Graham, F.M. (1987) Levels of oxytocin-like activity and progesterone in follicular fluid from *in vitro* fertilization cycles. *J. In Vitro Fertil. Embryo Transf*., **4**, 103–106.

Schaeffer, J.M., Liu, J., Hsueh, A.J. and Yen, S.S.C. (1984) Presence of oxytocin and arginine vasopressin in human ovary, oviduct, and follicular fluid. *J. Endocrinol. Metab*., **59**, 970–973.

Snijders, M.P.M.L., de Goeij, A.F.P.M., Debets-Te Baerts, M.J.C. *et al*. (1992) Immunhistochemical analysis of oestrogen receptors and progesterone receptors in the human uterus throughout the menstrual cycle and after the menopause. *J. Reprod. Fertil*., **94**, 363–371.

Soloff, M.S. (1989) Endocrine control of parturition. In Wynn, R.M. and Jollie, W.P. (eds), *Biology of the Uterus*. Plenum Medical Book Company, New York, pp. 559–607.

Soloff, M.S. and Hinko, A. (1993) Oxytocin receptors and prostaglandin release in rabbit amnion. *Ann. N.Y. Acad. Sci*., **689**, 207–218.

Takemura, M., Nomura, S., Kimura, T. *et al*. (1993) Expression and localisation of oxytocin receptor gene in human uterine endometrium in relation to the menstrual cycle. *Endocrinology*, **132**, 1830–1835.

Telfer, J.F., Lyall, F., Norman, J.E. and Cameron, I.T. (1995) Identification of nitric oxide synthetase in human uterus. *Hum. Reprod*., **10**, 19–23.

Telfer, J.F., Irvine, G.A., Kohnen, G. *et al*. (1997) Expression of endothelial and inducible nitric oxide synthase in non-pregnant and decidualized human endometrium. *Mol. Hum. Reprod*., **3**, 69–75.

Tjugum, J., Norstrom, A., Dennefors, B. and Lundin, S. (1986) Oxytocin in human follicular fluid and its possible role in the ovulatory process as studied *in vitro*. *Hum. Reprod*., **1**, 283–286.

Wallace, J.M., Helliwell, R. and Morgan, P.J. (1991) Autoradiographical localization of oxytocin binding sites on ovine oviduct and uterus throughout the oestrous cycle. *Reprod. Fertil. Dev.*, **3**, 127–135.

Werth, R. and Grusdew, W. (1898) Untersuchungen über die Entwicklung und Morphologie der menschlichen Uterusmuskulatur. *Arch. Gynäkol*., **55**, 325–409.

Wetzstein, R. (1965) Der Uterusmuskel: Morphologie. *Arch. Gynecol*., **202**, 1–13.

Wildt, L., Kissler, S., Licht, P. and Becker, W. (1998) Sperm transport in the human female genital tract and its modulation by oxytocin as assessed hysterosalpingoscintigraphy, hysterotonography electrohysterography and Doppler sonography. *Hum. Reprod. Update*, **4**, 655–666.

Zingg, H.H., Rosen, F., Chu, K. *et al*. (1995) Oxytocin and oxytocin receptor gene expression in the uterus. *Rec. Prog. Hormone Res*., **50**, 255–273.