Article

Oxytocin – a stimulator of directed sperm transport in humans

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Abstract

Rhythmic peristaltic contractions of the muscular wall of the non-pregnant uterus, as well as rapid sperm transport from the vagina to the Fallopian tubes, have long been documented by means of vaginal sonography and hysterosalpingoscintigraphy. Uterine peristaltic activity reaches a maximum before ovulation and is controlled via oestradiol secretion from the dominant follicle systemically and into the utero–ovarian countercurrent system; it is also enhanced by oxytocin. In this study, the effect of oxytocin and its receptor antagonist atosiban on uterine peristalsis and thus directed sperm transport during the mid and late follicular phases was examined. Atosiban did not show any effect either on frequency or on pattern of the peristaltic contractions. However, oxytocin significantly increased the rapid and directed transport of radiolabelled particles representing spermatozoa from the vagina into the Fallopian tube ipsilateral to the site of the dominant follicle (P = 0.02, 0.04 and 0.02 after 1, 16 and 32 min of documentation respectively). It seems reasonable to assume that oxytocin plays an important, although not critical, role in the mechanisms governing rapid sperm ascension that, at least in humans, were developed to rapidly preserve an aliquot of spermatozoa following intercourse.

Keywords: *atosiban, oxytocin, sperm transport, 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 spermatozoa-size have been shown to migrate 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, is controlled by oestradiol secretion from the dominant follicle systemically and into the utero–ovarian countercurrent system (Oike *et al*., 1988; Maggi *et al*., 1992; Bulletti *et al*., 1993; Kunz *et al*., 1998a,b). Systemically applied oxytocin (OT) increased the frequency of uterine peristaltic contractions during the early and mid-follicular phases (Kunz *et al*., 1998b; Wildt *et al*., 1998). However, only those contraction waves directed towards the fundal part of the uterus, i.e. cervico–fundal peristaltic waves, were significantly stimulated by oxytocin, but not waves with fundal–cervical orientation (Kunz *et al*., 1998b). One aim of the present study was to answer the question whether the increase of cervico–fundal contractile activity subsequent to an OT injection also stimulates passive and directed sperm transport, and it was of special interest whether the OT receptor (OTR) of the non-pregnant uterus plays a critical role in the control of uterine peristalsis during the follicular phase of the menstrual cycle. If the OTR plays a critical role in uterine peristalsis, could administration of the oxytocin receptor antagonist atosiban decrease the hyperperistalsis commonly observed in women suffering from endometriosis?

Materials and methods

Patients

A total of 17 women aged 28–34 years (mean 31) either with sterility due to andrological reasons (13 healthy women, study 1 and 2) or suffering from endometriosis and infertility (4 women, study 1) entered the studies after giving informed and written consent. In all patients laparoscopies had been performed previously, and all 17 patients experienced regular and ovulatory cycles. By means of vaginal sonography, the present menstrual cycle of all patients was observed during the follicular phase, in order to document normal follicular development and localization, as well as ovulation preceding the luteal phase. Assignment to the respective phases of the menstrual cycles was according to the results of hormone measurements and to the sonographical documentation (Logiq 500; Kranzbühler, Solingen, Germany) of the dominant ovarian structure. Women with a history of ovariectomy, of uterine fibroids, or of malformations were excluded from the studies.

Study design

Study 1: VSUP with atosiban

Eight women participated in the study with atosiban administration (phase II clinical study ATCP98–1: The effect of atosiban on uterine peristalsis of the non-pregnant uterus of healthy women and women with diagnosed endometriosis; Ferring AB, Malmö, Sweden, 1998–2000). Four women were healthy and four women suffered from endometriosis and infertility (one woman with grade I and three women with grade IV endometriosis, according to the revised classification of the American Society of Reproductive Medicine (1997).

The effects of atosiban administration on uterine peristalsis were examined during the mid and late follicular phases of the cycles. The assignment to the respective phases of the menstrual cycle was according to hormone and follicular measurements, which were determined immediately prior to the start of the study in each patient.

Following the determination of baseline uterine peristaltic activity by means of vaginal sonography, an injection needle was placed intravenously. Then 6.75 mg of the oxytocin antagonist atosiban (1-deamino-2D-Tyr(OET)-4-Thr-8-Orn-vasotocin/oxytocin; Ferring AB, Malmö, Sweden) was injected intravenously over 30–60 s, followed immediately by a permanent infusion of 300 μg atosiban per minute over maximal 60 min duration.

Vaginal sonography of uterine peristalsis (VSUP) was performed every 15 min during the 1 h infusion time of atosiban. The frequencies and patterns of uterine peristalsis obtained during atosiban administration were compared with the pre-atosiban baseline peristaltic uterine contractions. Hence, the women in the atosiban study served as their own controls.

Vaginal sonography of uterine peristalsis (VSUP)

VSUP was performed with a 7.5 Mhz probe (Logiq 500; Kranzbühler, Solingen, Germany) as published previously (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 precise estimation of the frequency of the contraction waves the tape was replayed at 5 times regular speed. This also allowed the determination of the direction of the waves. 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.

Study 2: Hysterosalpingoscintigraphy with oxytocin (OT-HSSG)

Between 1994 and 1996, hysterosalpingoscintigraphy (HSSG) was performed in nine women with an oxytocin bolus injection during the early and mid-follicular phases of the regular cycles according to the methods described (Kunz *et al*., 1996). The results of HSSG obtained from 64 women during the follicular phase of their menstrual cycle (Kunz *et al*., 1996; Leyendecker *et al*., 1996) served as controls.

Prior to ovulation, intensity and frequency of the subendometrial myometrium reach a maximum consisting of predominantly cervico-fundal contractions (Kunz *et al*., 1996) which could not be exceeded by OT, presumably due to a refractoriness of the subendometrial myometrium (Kunz *et al*., 1998b). Because of this, OT-HSSG was not performed prior to ovulation.

Hysterosalpingoscintigraphy (HSSG)

While the women lay in a supine position immediately prior to the administration of the radiolabelled (^{99m}technetium) albumin macrospheres of sperm size (Solco MAA; Nuclear GmBH, Grenzach-Wyhlen, Germany) into the dorsal fornix of the vagina, a bolus of 3 IU of oxytocin (Syntocinon®, Sandoz AG, Nürnberg, Germany) was injected intravenously. The time between the injection of the oxytocin and the vaginal deposition of the macrospheres never exceeded 30 s. The ascension of the macrospheres from 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 from the first minute until 32 min after administration. For the assessment of the ascension, the genital tract was subdivided into four compartments. The site of application was compartment 1, the uterine cavity was compartment 2 and the Fallopian tubes were defined as compartment 3. Regions of interest referring to the compartments were determined and the counts within each compartment were measured and calculated as a 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.

Hormone measurements

From each woman, a venous blood sample was drawn for the measurement of the serum oestradiol, progesterone and LH concentrations, using commercially available enzyme

immunoassay kits (Serono Diagnostics GmBH, Freiburg, Germany).

Statistical analysis

Statistical analysis was performed using Student's *t*-test, and significance was assumed when $P < 0.05$ (Werner, 1989). Prior to the use of the Student's *t*-test, testing according to the equation for the normal distribution was performed (for further details, see Werner, 1989), revealing a normal distribution of the data.

Results

The results are presented in **Figures 1–3**. In all patients in studies 1 and 2, an ovulatory menstrual cycle could be documented. Follicular diameters, serum oestradiol and progesterone concentrations during the early, mid- and late follicular phases of the cycles are shown in **Tables 1** and **2**. The women in this study did not differ significantly from the healthy controls with respect to age, phase of cycle, diameter of the dominant follicle and sex hormone concentrations (for details, see Kunz *et al.*, 1996).

Study 1

The administration of atosiban did not lead to any discernable effect on frequency or pattern of uterine peristaltic activity either in the healthy women or in those suffering from endometriosis (**Figure 1**). Hyper- and dysperistaltic contractile activity in the women with endometriosis could be observed as published previously (Leyendecker *et al.*, 1996), but failed to reach statistical significance.

Study 2

The data from eight out of nine women could be analysed, four each during the early and mid-follicular phase.

Figure 2 depicts the findings of the present study provided by OT-HSSG obtained from the early follicular phases of the cycles in comparison with the corresponding results previously obtained from HSSG without OT application (Kunz *et al.*, 1996). The corresponding results of the OT-HSSG as documented during the mid-follicular phases are shown in comparison with the results of HSSG obtained from the mid-follicular and late follicular phases of the menstrual cycle respectively in **Figure 3**. The mean percentages of total radioactivity, representing the labelled albumin macrospheres within the female genital tract, are shown 1, 16 and 32 min after vaginal administration.

OT-HSSG in the early follicular phase

Following the injection of OT in the early follicular phases of the investigated women, the ascension of the macrospheres representing spermatozoa from the vagina into the isthmical parts of the Fallopian tubes (compartment 3) was significantly increased as compared with the healthy control during the 32 min time of documentation ($P = 0.002$).

OT-HSSG in the mid-follicular phase

The mid-follicular migration of the macrospheres from the vaginal depot through the uterine cavity up to the Fallopian tubes following OT bolus injection was again significantly increased as compared with the corresponding control ($P < 0.001$ for compartment 2 and $P < 0.001$ for whole compartment 3 from minutes 1–32 of documentation respectively), and thus similar to the ascension usually observed during the late follicular phases without OT (**Figure 3**; Kunz *et al.*, 1996).

In detail, OT bolus injection resulted in a clear and significantly increased orientation of the labelled albumin particles, particularly towards the isthmical parts of the tubes ipsilateral to the site of the dominant follicle as compared with the normal control with HSSG during the mid-follicular phase ($P = 0.02$, 0.04, 0,02 after 1, 16 and 32 min of documentation, respectively). Logically, the accumulation of the macrospheres

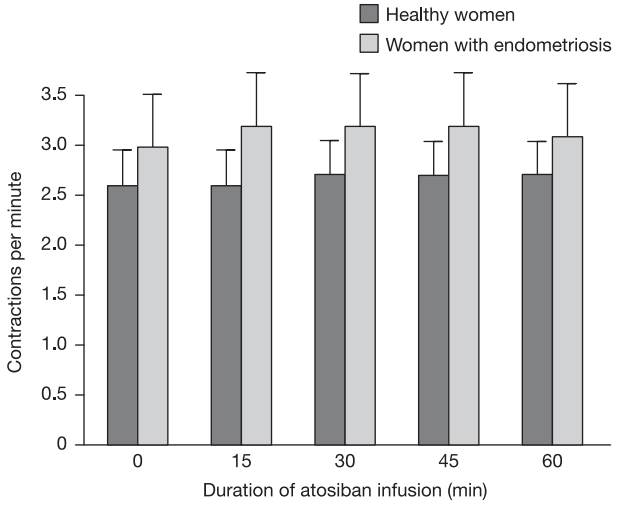

Figure 1. Graphical demonstration of the frequency of the subendometrial uterine peristaltic waves (mean ± SEM contractions/min) during the mid- and late follicular phase of normal menstrual cycles in healthy women and in women with endometriosis, each receiving atosiban. The i.v. administration of atosiban in high doses (6.75 mg initially, followed by 300 μg atosiban per minute over 60 min) did not exert any effect on frequency or pattern (not depicted) of uterine peristalsis. Women suffering from endometriosis showed a higher frequency of peristaltic waves as compared with the control, however not significantly. Cervico–fundal directed waves predominated (not depicted).

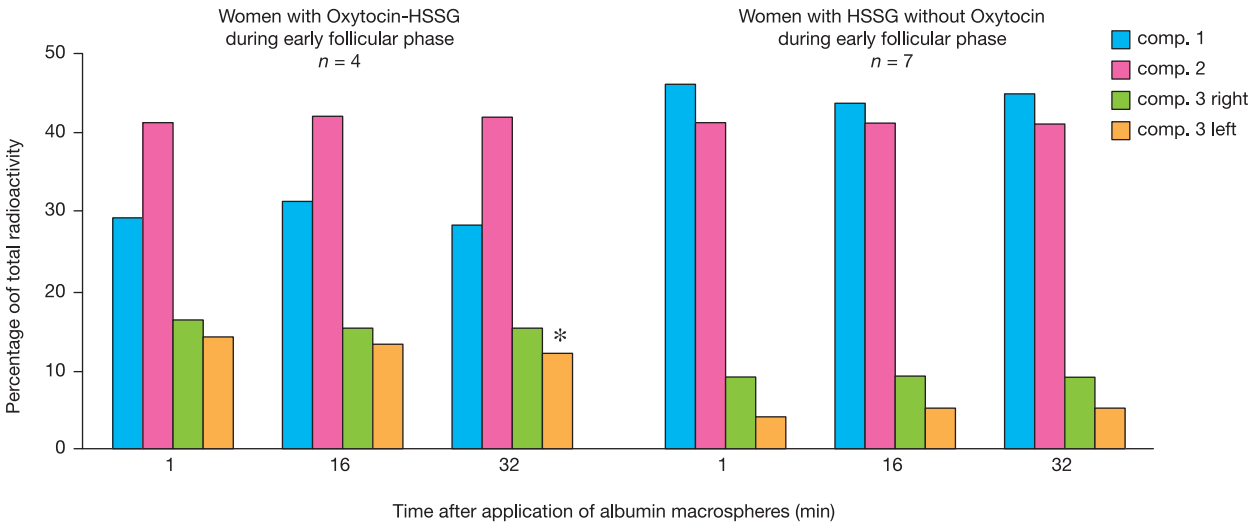

Figure 2. The distribution of the percentage of total counts, representing the labelled albumin macrospheres, within the female genital tract (compartments 1, 2 and 3 being the upper vagina, the uterine cavity and the isthmical part of the tubes, respectively) 1, 16 and 32 min after vaginal application during the early follicular phase of the normal cycles with oxytocin (left half) and without oxytocin (right half) by means of hysterosalpingoscintigraphy (HSSG). With respect to compartment 3, the right and left tubes were differentiated. Obviously, the injection of oxytocin resulted in a significantly increased migration of the radiolabelled particles representing spermatozoa into the tubes as compared with the controls (*, $P = 0.02$).

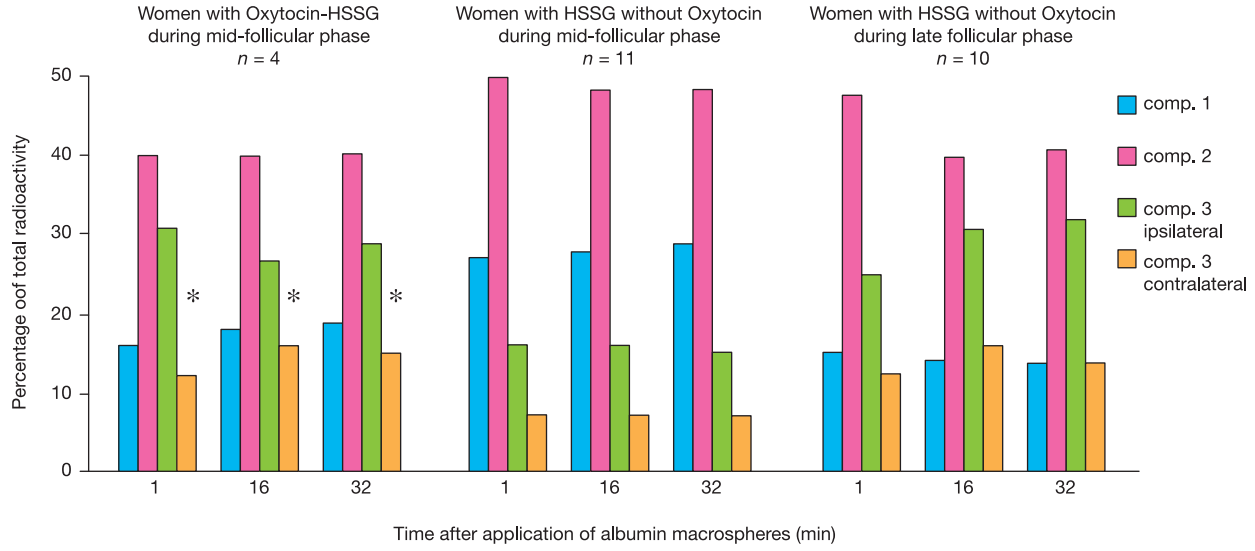

Figure 3. Distribution of the percentage of total counts, representing the labelled albumin macrospheres, within the female genital tract (compartments 1, 2 and 3 being the upper vagina, the uterine cavity and the isthmical part of the tubes respectively) 1, 16 and 32 min after vaginal application during the mid-follicular phase with oxytocin (left) and without oxytocin (middle) and during the late follicular phase without oxytocin (right) of the normal cycles. With respect to compartment 3, the right and left tubes were differentiated according to the side of the dominant follicle and were denominated as ipsilateral or contralateral. During the mid-follicular phase oxytocin resulted both in a significantly increased transport of radioactivity into the tubes ipsilateral to the dominant follicle as compared with the contralateral tube (*, $P = 0.003$, 0.02, 0.04 after 1, 16 and 32 min of documentation respectively) and as compared with the control ($P < 0.001$ for compartment 2 and $P < 0.001$ for whole compartment 3 from minutes 1 to 32 of documentation respectively). However, an apparent similarity of the relative distribution of the macrospheres within the uterine compartments between the women with oxytocin hysterosalpingo-scintigraphy (HSSG) during the mid-follicular phase and the control group of patients with HSSG without oxytocin during the late follicular phase can be seen, again with a clear orientation of the inert particles towards the tube ipsilateral to the localization of the dominant ovarian follicle.

Table 1. The diameter of the dominant follicle and the oestradiol and progesterone serum concentrations during the mid- and late follicular phases of the cycle in healthy women and women suffering from endometriosis, each receiving atosiban, examined by vaginal sonography of uterine peristalsis (values are mean ± SD).

Patient	n	*Follicular diameter (mm)*	*Serum oestradiol (pg/ml)*	*Serum progesterone (ng/ml)*
Healthy	4	14 ± 3	58 ± 27	0.6 ± 0.2
Endometriosis	4	17 ± 5	154 ± 110	0.4 ± 0.2

Table 2. The diameter of the dominant follicle and the oestradiol and progesterone serum concentrations during the early and the mid-follicular phases of the cycle in healthy women receiving oxytocin examined by hysterosalpingoscintigraphy (values are mean ± SD).

Phase of cycle	n	*Follicular diameter (mm)*	*Serum oestradiol (pg/ml)*	*Serum progesterone (ng/ml)*
Early follicular	4	<11	7.5 ± 5	0.45 ± 0.37
Mid-follicular	4	14.3 ± 1.3	46 ± 40.5	0.35 ± 0.24

representing spermatozoa following oxytocin administration within the 'dominant' tube also reached significance when compared with the mean radioactivity of the own contralateral side after 1, 16 and 32 min of documentation respectively (P = 0.003, 0.02, 0.04 respectively).

Discussion

By means of VSUP and HSSG, the pattern of uterine peristaltic contractions of the non-pregnant uterus and its effect on directed sperm transport could be documented non-invasively under different physiological and pathophysiological conditions (Itturalde and Venter, 1981; Birnholz, 1984; Lyons *et al.*, 1991; Steck *et al.*, 1991; Kunz *et al.*, 1996, 1998b; Leyendecker *et al.*, 1996; Fanchin *et al.*, 1998, 2001; Wildt *et al.*, 1998; Bulletti *et al.*, 2000; de Ziegler *et al.*, 2001; Van Gestel *et al.*, 2003; Bulletti and de Ziegler, 2005; Kissler *et al.*, 2005). There is compelling evidence that uterine contractions of the subendometrial myometrium or archimyometrium provide directed and sustained transport of spermatozoa towards the Fallopian tube located ipsilateral to the site of the dominant ovarian follicle. Directed transport capacities could also be observed during the luteal phase (Kunz *et al.*, 2006). Fibroids of the inner myometrium might influence the intrauterine migration of human pre-implantation embryos (Gianaroli *et al.*, 2005).

The present study revealed that the contractile activity of the human subendometrial myometrium during the mid- and late follicular phase could not be influenced by high dose administration of the receptor antagonist atosiban. However, oxytocin itself significantly stimulated rapid and directed sperm transport (for P-values see Results section), presumably via the stimulation of cervico–fundal directed uterine peristaltic contractions (Kunz *et al.*, 1998b).

Wildt and co-workers (1998) previously reported the effects of oxytocin on directed sperm transport, but as far as is known, the effect of atosiban on follicular phase uterine peristalsis beyond the menstrual period has not been examined before. The present study found similar results to Wildt *et al.*, but using a different schedule of oxytocin application. However, the results presented in this paper, together with previously published studies (Kunz *et al.*, 1996, 1998a,b) and a review of the literature, help to gain new insights in the mechanisms governing directed sperm transport in humans.

Uterine contractions of the non-pregnant uterus can be stimulated by a number of hormones and other mediators such as prostaglandins, vasopressin, oxytocin and peptides (Maggi *et al.*, 1992; Kunz *et al.*, 1998b; Wildt *et al.*, 1998). However, there is striking evidence that oestradiol, secreted systemically as well as into the utero–ovarian countercurrent system, plays a critical role in the control and function of uterine peristaltic activities during the menstrual phases (Bulletti *et al.*, 1993; Kunz *et al.*, 1998a,b). The stimulating effect of oestradiol on frequency and intensity of uterine contractions during the menstrual cycle comprises a cascade of effects on the levels of transcription, translation and post-translation of the smooth muscle cell with the synthesis of growth factors, enzymes and hormones predominantly such as oxytocin and its receptor (Katzenellenbogen *et al.*, 1979; Cole and Garfield, 1989; Sheldrick and Flick-Smith, 1993; Batra, 1994; Phaneuf *et al.*, 1995; Sanborn *et al.*, 1995; Zingg *et al.*, 1995a,b). Human OTR-mRNA has been detected within the non-pregnant myometrium (Fuchs *et al.*, 1985; Maggi *et al.*, 1992; Kimura, 1995) and within the endometrium, with a maximum around ovulation (Takemura *et al.*, 1993). In the marmoset monkey, a tendency towards an increased OTR-expression around the time of ovulation within the subendometrial myometrium was observed (Einspanier, 1998).

While serum OT concentrations did not exhibit a pulsatile or cycle-dependent pattern (Challinor *et al.*, 1994), in addition to its classic hypothalamic site of production, synthesis of OT has also been demonstrated within the endometrium and the ovary respectively (Garcia Villar *et al.*, 1983; Schaeffer *et al.*, 1985; Tjugum *et al.*, 1986; Peek *et al.*, 1987; Okuda 1992; Fortune and Voss, 1993; Furuya *et al.*, 1995a,b; Ivell *et al.*, 1995; Khan-Dawood *et al.*, 1995; Zingg *et al.*, 1995b; Fuchs *et al.* 1998).

One aim of this study was to examine whether the OT-OTR system of the non-pregnant uterus plays a critical role in the control of uterine peristalsis during the follicular phase of the menstrual cycle. In the present study, atosiban was given to patients in the same dose as it is used in order to stop preterm labour during pregnancy. At this dosage, atosiban very effectively inhibited preterm uterine labour through occupation of the OTR

(Ferring, Malmö, Sweden; Rath and Bartz, 2005), although the myometrial expression of OTR-mRNA is more than 100-fold higher in the pregnant human myometrium as compared with the myometrium of the non-pregnant uterus (Kimura, 1995, 1998). Hence it has to be assumed that the doses of atosiban used in this study should have occupied all uterine OTR and vasopressin receptors (Manning *et al.*, 1995). However, atosiban did not demonstrate any inhibitory effect on the peristaltic contractions during the mid and late follicular phase either in healthy women or in women suffering from endometriosis. Therefore, the OT-OTR pathway appears not to be critical during the mid and late follicular phases of the menstrual cycle for the maintenance of continuous uterine peristaltic activity, as usually observed during the follicular phase in healthy women and in women suffering from endometriosis and sterility (Itturalde and Venter, 1981; Birnholz, 1984; Lyons *et al.*, 1991; Kunz *et al.*, 1996, 1998b; Leyendecker *et al.*, 1996; Fanchin *et al.*, 1998, 2001; Wildt *et al.*, 1998, Bulletti *et al.*, 2000, de Ziegler *et al.*, 2001; Van Gestel *et al.*, 2003; Bulletti and deZiegler, 2005; Kissler *et al.*, 2005). It has to be assumed that oestradiol secreted from the dominant follicle controls the uterine peristalsis of the non-pregnant uterus via different pathways than the OT-OTR pathway (Kunz *et al.*, 1998b). The observation that oestradiol alone increased the frequency of uterine contractions when added to the medium of extracorporal perfused human uteri confirms this assumption (Bulletti *et al.*, 1993).

Hyper- and dysperistalsis is a phenomenon commonly observed in women suffering from endometriosis and sterility, resulting in a breakdown of directed sperm transport with subsequent sterility (Leyendecker *et al.*, 1996, 1998, 2006; Bulletti *et al.*, 2000, 2001; Kunz *et al.*, 2000, 2005). Thus, one aim of the atosiban pilot study (phase II clinical study ATCP98–1: The effect of atosiban on uterine peristalsis of the non-pregnant uterus of healthy women and women with diagnosed endometriosis; Ferring AB, Malmö, Sweden) was to examine whether uterine peristaltic activity in women suffering from endometriosis and sterility might be inhibited by atosiban. If this were the case, the hyper- and dysperistalsis causing the sterility observed in women suffering from endometriosis (Leyendecker *et al.*, 1996) might be reduced with atosiban. The women with endometriosis in the present study exhibited an increased frequency of uterine contractions as compared with the healthy control as published previously (Leyendecker *et al.*, 1996; Bulletti *et al.*, 2001; Vercelini *et al.*, 2005); however, statistical significance was not reached in this study due the low number of patients examined. Nevertheless, atosiban showed no effect on the uterine peristalsis in endometriosis.

All kinds of uterine peristaltic contractions of the non-pregnant uterus are confined to the subendometrial myometrium or archimyometrium (Kunz *et al.*, 1996, 2006). 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, therefore termed neomyometrium (Werth and Grusdew, 1898), the origin 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, 1998a; Noe *et al.*, 1999). Thus directed passive transport of spermatozoa (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 (Einer-Jensen, 1988; Einer-Jensen *et al.*, 1989; Kunz *et al.*, 1998a; Mueller *et al.*, 2006). Surprisingly, oxytocin stimulated directed sperm transport, although given systemically. The underlying mechanisms are unknown. An asymmetrical side-different and specific response of the archimyometrium to oxytocin with respect to the localization of the dominant follicle offers one explanation. On the other hand, it has been shown that prior to ovulation a mucus plug is formed within the isthmical part of the tube (Jansen, 1980). The microstructure of the mucus plug was influenced by oestrogen and progestin (Jansen, 1980). It is quite possible that the mucus plug of the 'contralateral' tube develops a different viscosity as compared with the plug of the 'dominant' tube as a consequence of the side-specific different amounts of sex steroids derived from the dominant ovarian structure offered to the tubes and uterine horns via the utero–ovarian vascular counter-current system (Einer-Jensen, 1988, 1989; Kunz *et al.*, 1998b). Hence, the mucus plug in the isthmical part of the tube contralateral to the dominant follicle would serve as an obstacle to the rapid and passive transport of spermatozoa into this tube as compared with the 'dominant' side.

In conclusion, oxytocin may not play a critical role in the control of the continuous wave-like activity of the archimyometrium during the follicular phase, like oestradiol (Kunz *et al.*, 1998b), but appears to be a very potent and fast stimulator of uterine contractions (Kunz *et al.*, 1998b; Wildt *et al.*, 1998) resulting in an impressive and immediate increase of rapid and directed sperm transport. Besides its synthesis within the endometrium and dominant follicle (Garcia Villar *et al.*, 1983; Schaeffer *et al.*, 1985; Tjugum *et al.*, 1986; Peek *et al.*, 1987; Okuda *et al.*, 1992; Furuya *et al.*, 1995a,b; Ivell *et al.*, 1995; Khan-Dawood *et al.*, 1995; Fuchs *et al.*, 1998), oxytocin is released from the posterior lobe of the pituitary gland in response to vaginal distension and in response to tactile as well as emotional stimuli (Fox *et al.*, 1970; Fox and Fox, 1971; Fox, 1973, 1976; Carmichael *et al.*, 1987; Murphy *et al.*, 1987; Gilbert *et al.*, 1991). It is tempting to speculate from a phylogenetical point of view that in humans, along with the development of walking erect, the ejaculate deposited in the vagina was at risk of being spilled out. So it seems reasonable to assume that mechanisms of rapid sperm ascension, at least in humans, developed as a way to preserve an aliquot of spermatozoa. The rising oestradiol secretion derived from the growing dominant follicle systemically, as well as into the ipsilateral utero–ovarian countercurrent system, provides a permanent readiness of the uterine peristaltic pump with respect to rapid and directed sperm transport. Oxytocin, its concentration increased locally as well as systemically by the vaginal stimuli of sexual intercourse, might additionally,

although not crucially, stimulate the activity of the uterine peristaltic pump in order to increase rapid and directed sperm ascension from the vagina towards the sperm depots of the uterine cervix and the isthmical parts of the Fallopian tubes (Jansen 1980; Kunz *et al*., 1996). The fact that OT stimulated rapid sperm ascension not only in general but particularly into the Fallopian tube ipsilateral to the ovary bearing the dominant follicle deserves special attention.

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