

MODULATION OF UTERINE CONTRACTILITY AND PERISTALSIS BY OXYTOCIN IN ESTROGEN-PRIMED NON-PREGNANT SWINE UTERI

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Abstract

Oxytocin is one of the most potent uterotonic agents and is known to fluctuate throughout the menstrual cycle, showing an increase during sexual stimulation and arousal, with a peak during orgasm in women. To date, limited data are available on the effects of oxytocin on the regulation of uterine contractility and transport mechanisms in human reproduction. The goal of this study was to evaluate the effects of oxytocin on uterine contractility and peristalsis in estrogen-primed non-pregnant uteri. In an extracorporeal perfusion model of the swine uterus the effect of dynamic changes in uterine contractility and peristalsis in response to oxytocin and estrogen administration was observed. Spontaneous uterine contractility and oxytocin-induced uterine contractility and peristalsis with and without estrogen perfusion were assessed using an intrauterine double-chip microcatheter. Spontaneous peristalsis and oxytocin induced contraction waves without estrogen perfusion resulted in a slightly higher intrauterine pressure in the isthmus uteri in comparison with the corpus uteri, while the peristaltic waves were seen to start mostly in the corpus uteri, moving in the direction of the cervix. While after estrogen perfusion oxytocin produced a significant increase in intrauterine pressure in the isthmus uteri compared to the corpus uteri, and 80% of the peristaltic waves started in the isthmus uteri, moving in the direction of the corpus uteri. This observation strengthens the view that oxytocin is able to support directed transport mechanism in the female genital tract only in the presence of estrogens. The biological role of oxytocin increase during sexual stimulation and arousal with a peak during orgasm for the mechanisms of reproduction may be to stimulate directed uterine transport mechanisms in the presence of estrogens.

Key words: oxytocin, uterine contractility, peristalsis, sperm transport, perfusion, fertility

INTRODUCTION

Oxytocin levels fluctuate throughout the menstrual cycle and correlate with genital lubrication in women; they are therefore believed to play a role in the peripheral activation of sexual function [1]. The suppression of endogenous oxytocin activity in women affects the ovulatory cycle [2]. Evans et al. [2] have also demonstrated a biological correlation between oxytocin and

the physiological processes of luteinizing hormone (LH) regulation in animal models. Recently, Benousaidh et al. [3] reported that in rats, oxytocin modulates the activity of the uterus in a cycle-dependent fashion. Oxytocin is one of the most potent uterotonic agents and exerts a wide spectrum of central and peripheral physiological effects. It is used clinically to induce labor at term [4, 5]. Oxytocin also plays a role in the initiation and maintenance of successful lactation in humans and is involved in milk ejection from the mammary glands [6-9]. Several studies have shown that oxytocin levels increase during sexual stimulation and arousal, with a peak during orgasm, in women and in men [7, 10-13].

The orgasm-related increases in oxytocin levels in the presence of estrogens may play an important role on directed transport mechanisms in the female genital tract. Adequate uterine contractility is involved in the transport of semen and gametes and in successful embryo implantation, while inadequate uterine contractility may lead to ectopic pregnancies, miscarriages, retrograde bleeding, and endometriosis [14-16]. Normally, uterine contraction waves show the highest frequencies and amplitudes with cervicofundic peristalsis during the periovulatory phase, when estrogen is the dominating hormone [17-18]. In women with intact periovulatory uterotubal transport function as assessed by hysterosalpingoscopy (HSSG), the pregnancy rate achieved spontaneously or by intrauterine insemination was found to be significantly higher than in women with a negative transport assessment [19-20]. This periovulatory cervicofundic peristalsis has been described as "rapid sperm transport" to the side bearing the dominant follicle, which is a precondition for successful reproduction in humans [19-22].

The original extracorporeal perfusion model of an isolated uterus was first described by Bulletti et al. [23]. Previous investigations validated the feasibility of this perfusion model of isolated uteri for various purposes [24-36]. This perfusion model is able to keep the swine uterus in a functional condition and is suitable for the study of physiological questions [34-36]. This experimental system can detect intrauterine pressure changes due to mechanical contractions of the organ, as it maintains the architecture and intercellular relations of the uterus [37]. The extracorporeal perfusion model of an isolated non-pregnant swine uterus may therefore be appropriate for the evaluation of uterine transport mechanisms due to different test substances.

The aim of this study was to evaluate the effects of oxytocin in the presence of estrogens in the regulation of uterine contractility and peristalsis which serves as a model for simulation of directed transport mechanisms through the female genital tract. The advantage of the used animal model is that a large number of uteri equally in size and condition from young and healthy animals in their reproductive lifespan could be tested. Using uteri from young mammals offers the possibility to detect definite differences in contraction peaks between distal and proximal uterus compartments.

MATERIALS AND METHODS

Swine (*Sus scrofa domestica*) are widely used in research. The swine uterus is a long bicornuate uterus with a single corpus and a single cervix. The uterine wall has a similar architecture to that of humans and other domestic animals, with the three classical histological elements of the uterine wall, including endometrium; myometrium which consists of clearly oriented smooth muscle cells; and perimetrium. The endometrium contains many hundreds of glands in a cross-section of the uterine wall and the myometrium is clearly differentiated into inner circular and outer longitudinal layers. The fallopian tubes in the adult female have the same diameter as those in humans. However, they are much longer, and the uterine corpus is also longer in comparison with human uteri. The sow has an estrous cycle of 20–21 days.

Sixty swine uteri were obtained from the local slaughterhouse. The uteri were selected on the basis of their size and overall condition, as well as the condition of the uterine arterial stumps. The mean weight of the swine uteri was 123 g (range 81.5–161.8 g). They all came from healthy animals aged 5–18 months. Swine uteri are very easily separated from the rest of the body within approximately 2 min shortly after the animal is killed by electric shock (1.5 A, 400 V, 4 s).

PERFUSION SYSTEM

After catheter placement in the uterine vessels with 16–24-gauge needles (Abbocath-T; Abbott Ireland, Sligo, Ireland), depending on the uterus size, the organ was placed in a controlled-temperature perfusion chamber (Karl Lettenbauer, Erlangen, Germany) filled with the perfusion medium. The uterus was then connected bilaterally with two reservoirs containing the perfusion buffer (Krebs–Ringer bicarbonate glucose buffer, Sigma, Deisenhofen, Germany). The perfusion medium was oxygenated with carbogen gas (a mixture of 95% oxygen and 5% carbon dioxide) and then forced into the uterine arterial catheters with two roller pumps. The flow rate of the perfusion medium was constantly monitored and kept at 15 mL/min and 100 mmHg.

VITALITY PARAMETERS

Perfusate samples were taken at 1-hour intervals for measurement of pH, PO₂, PCO₂, HCO₃⁻, lactate, and oxygen saturation. The perfusate samples were ana-

lyzed using an i-STAT portable clinical analyzer (Abbott Diagnostics, Abbott Park, Illinois, USA).

INTRAUTERINE PRESSURE MEASUREMENT

Intrauterine pressure was recorded using an intrauterine double-chip microcatheter (Urobar 8 DS-F, Raumedic, Muenchberg, Germany) with a distance of 8 cm between the two pressure sensors. One sensor was placed in the isthmus uteri and the other was placed in the corpus uteri in the swine uterus. The fallopian tubes and cervix uteri were not closed. The double-chip microcatheter was connected to a Data-logger (MPR1, Raumedic, Muenchberg, Germany) for continuous monitoring of intrauterine pressure at both locations, with the data being transferred to a personal computer.

SPONTANEOUS UTERINE CONTRACTIONS

Spontaneous uterine contractions were achieved by adding calcium chloride (Sigma, Deisenhofen, Germany) to the perfusion medium at a concentration of 500 mg/L.

INDUCTION OF UTERINE CONTRACTIONS

Oxytocin (Syntocinon; Novartis Germany Ltd., Nuremberg, Germany) at increasing dosages of 0.1, 0.3, and 1 IU, was used to induce contractions of the uterus every 15 min until regular uterine contractions occurred. The medication was administered as bolus injections through the uterine arterial catheters.

ESTROGEN PERFUSION

For the estrogen perfusion 17-beta estradiol in a concentration of 25 pg/ml and 50 pg/ml was added to the perfusion medium and uteri were perfused for one hour before starting oxytocin administration for induction of regular uterine contractions.

STATISTICAL ANALYSIS

A paired *t*-test was used for statistical evaluation of pressure increases during uterine contractions in the isthmus uteri in comparison with the corpus uteri. Pressure differences between the different concentrations of test substances were evaluated using analysis of variance (ANOVA). It was also assessed whether uterine contractions started in the isthmus uteri or in the corpus uteri. All calculations were performed using the Statistical Program for the Social Sciences (SPSS, version 10.1 for Windows; SPSS, Inc., Chicago, Illinois, USA). P values of less than 0.05 were considered statistically significant.

RESULTS

The experiments were only carried out when it was possible to maintain constant flow rates of the perfusion medium of 15 mL/min through each artery, with an ideal pressure of 100 mmHg, throughout the duration of the experiments. The vitality parameters re-

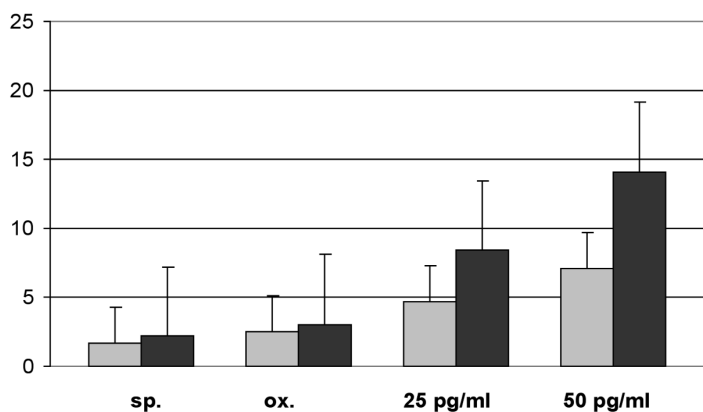


Fig. 1. Increases in intrauterine pressure (IUP), shown as means and standard deviation (SD). There were no differences between IUP in the Corpus uteri compared to isthmus uteri during spontaneous contractions = sp. ($P = 0.09$), and during oxytocin induced contractions without estrogen perfusion = ox. ($P = 0.1$). After perfusion with 25 pg/ml 17-beta estradiol the IUP increased significant higher in the isthmus uteri in comparison with corpus uteri after oxytocin administration ($P < 0.001$). After perfusion with 50 pg/ml 17-beta estradiol the IUP increased significant higher in the isthmus uteri in comparison with corpus uteri after oxytocin administration ($P < 0.001$). (Gray: corpus uteri; black: isthmus uteri. Each group included 15 perfused uteri.)

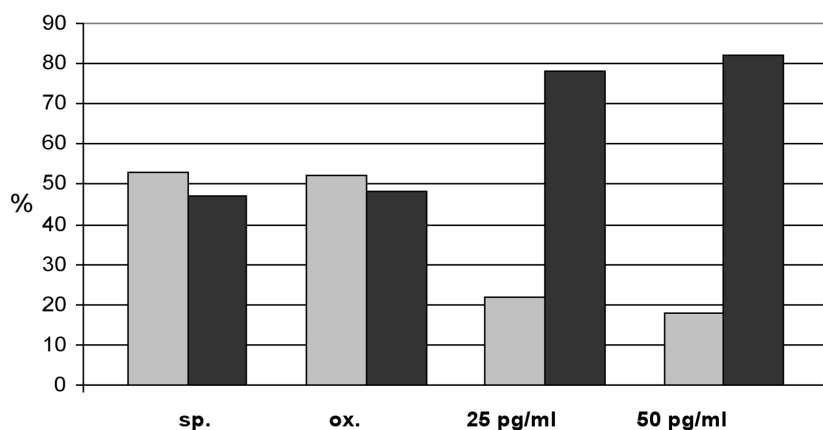


Fig. 2. Start of uterine peristalsis in the corpus uteri and isthmus uteri during spontaneous and oxytocin induced contraction waves in the absence of estrogens. After estrogen perfusion (25 pg/ml and 50 pg/ml) oxytocin was able to induce peristaltic waves starting in the isthmus uteri with a direction moving toward the corpus uteri (Gray: corpus uteri; black: isthmus uteri. each group included 15 perfused uteri.).

mained physiological during the first 8 hours of perfusion (data not shown; for details, see [34-36]).

Regularly recurring peristaltic waves, with IUP increases in both the corpus uteri and the isthmus uteri, were achieved in all of the perfused swine uteri. In general, there was no significant IUP increase during spontaneous contraction waves and oxytocin induced contraction waves in the absence of estrogen. The difference between IUP measured in the isthmus uteri and corpus uteri was also not significant in both groups. No directed peristalsis could be observed under these conditions.

After perfusion with 17-beta estradiol a dose dependent increase in IUP in the isthmus uteri and the corpus uteri was observed following oxytocin administration, respectively. The IUP increase in the isthmus uteri was statistically significant higher compared to the corpus uteri in a dose dependent manner (Fig.1). In addition, 17-beta estradiol perfusion resulted in a significant increase in peristalsis starting in the isthmus uteri and moving in the direction of the corpus uteri (Fig. 2).

DISCUSSION

This study investigated intrauterine pressure gradients and peristaltic waves during spontaneous contractions, oxytocin induced contraction waves and the effects of oxytocin administration after estrogen perfusion of isolated non-pregnant swine uteri. For the first time, intrauterine pressure gradients and peristaltic waves

starting in one compartment of the uterus were measured using a double-chip microcatheter. During spontaneous and oxytocin induced uterine contractions no directed peristalsis or pressure gradients were observed. While in the presence of estrogen oxytocin was able to generate contractions and peristaltic waves resulting in a significant increase in IUP in the isthmus uteri in comparison with the corpus uteri. Furthermore 80 % of the peristaltic waves started in the isthmus uteri with a direction toward the corpus uteri.

These results may be an explanation for the observations of some clinical studies. In women with intact periovarian uterotubal transport function as assessed by HSSG, the pregnancy rate achieved spontaneously or by intrauterine insemination was found to be significantly higher than in women with a negative transport assessment [19, 20]. This periovarian cervicofundic peristalsis has been described as "rapid sperm transport" to the side bearing the dominant follicle, which is a precondition for successful reproduction in humans [19-22]. Richter et al. recently described, that estrogens are able to increase immunohistochemical reactivity of myometrial oxytocin receptors and of contractile reactivity of the myometrium in extracorporeally perfused human uteri [28, 30].

Therefore oxytocin levels increased during sexual stimulation and orgasm in the presence of estrogen may be important for the successful regulation of uterine peristalsis in reproduction. The present results provide evidence for the concept that oxytocin may support cervicofundic peristalsis, resulting in a more

effectively directed sperm transport mechanism from the cervix to the upper part of the uterus and to the fallopian tubes [22]. The biological role of orgasm-related increases in oxytocin levels may therefore not only be important for sexual desire, but also for the induction of directed sperm transport to the side bearing the dominant follicle.

But on the other hand, is there really a biological need for a rapid sperm transport mechanism? There is evidence that after orgasm, the motility of the human uterus may be suppressed [38]. This would be likely to reduce the speed of sperm transport. In addition, the ejaculate needs time to decoagulate [39]. Human spermatozoa are unable to fertilize an ovum immediately after ejaculation; they require time to undergo a process called capacitation, and it is only after this process that the sperm is able to fertilize the ovum [40]. All of these mechanisms may promote a continuous and measured flow of capacitated spermatozoa to the fallopian tube; Levin [41] describes this importance of delayed sperm transport. Orgasm occurs with vaginal and uterine contractions and may be misinterpreted as powering rapid sperm transport to facilitate fertilization, but such fast transport would lead to the tubal deposition of non capacitated, incompetent spermatozoa. Therefore it may be speculated that prostaglandins contained in the seminal plasma may also be involved in the regulation of uterine contractility and thus in the regulation of uterine transport mechanisms. Prostaglandins may be the counterpart of oxytocin to tone the oxytocin effects regarding uterine contractility.

On the basis of the present results, oxytocin caused greater contractility and directed peristalsis of the uterus in the presence of estrogens when compared to oxytocin administration without estrogen perfusion and compared to spontaneous contractions. This may support further sperm transport into the fallopian tube at the time of ovulation when estrogens are the dominating hormones. Two methods have been used to assess uterine contractions *in vitro* and *in vivo*. The first involves direct intrauterine pressure measurement using a single invasive probe that is placed in the uterine cavity [16, 34–36]. However, while this method allows assessment of frequencies and increases in intrauterine pressure, it does not provide any information about the direction of peristalsis or pressure gradients, as the pressure is assessed at a single location with a single probe. The second method involves indirect assessment of contraction waves derived from various forms of visualization of uterine peristalsis during transvaginal ultrasound examinations or using ultrafast magnetic resonance imaging [42–45].

Continuous monitoring of intrauterine pressure, using multiple probes at different locations in the uterine cavity, may be more useful for evaluating directed uterine peristalsis and pressure gradients that can cause directed transport mechanisms. A double-chip microcatheter with two pressure sensors, of the type normally used for urodynamic examination of the bladder and urethra, may therefore be appropriate for investigating uterine contractility.

For the *in vitro* study of uterine transport mechanisms caused by peristaltic contractions and waves and

their regulation, the swine uterus may be useful, as the swine uterus is more analogous to a muscular tube. Peristaltic waves are easy to visualize, and these peristaltic waves are easy recordable using the intrauterine microchip catheter [46]. This may be due to the differences in the uterine cavity, which is more elongated in the swine uterus than in the human uterus. Delayed pressure changes may therefore be easier to detect using intrauterine multichip microcatheters in the swine uterus. In the case of cervicofundic peristalsis, it can be expected that the increase in IUP would start first in the lower part of the uterus (the cervix or isthmus uteri), with the increase in IUP later becoming detectable in the upper part of the uterus (the corpus or fundus uteri). In the case of fundocervical peristalsis, an opposite movement in the IUP can be expected to develop [47].

In fertile women the spontaneous pregnancy rate should be elevated in women achieving greater sexual arousal and orgasm compared to women without orgasm. But the problem is how to measure sexual arousal and orgasm levels. On the other hand oxytocin administration during artificial insemination should also raise pregnancy rate. But the needed concentrations and application ways are still unknown.

In summary, oxytocin in the presence of estrogens modifies uterine contractility in a characteristic way. Oxytocin appears to stimulate cervicofundic peristalsis, leading to a cervicofundic pressure gradient. Physiological observations in conjunction with the data presented suggest that both oxytocin and estrogen are important modulators of uterine contractility and transport mechanisms. The exact interactions of the involved mediators managing sperm transport in humans are still unknown. More knowledge in this field would enable a clinical application of the mediators to increase pregnancy rates in infertile couples.

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REFERENCES

1. Salonia A, Nappi RE, Pontillo M, Daverio R, Smeraldi A, Briganti A, Fabbri F, Zanni G, Rigatti P, Montorsi F (2005) Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. *Horm Behav* 47: 164–169
2. Evans JJ, Reid RA, Wakeman SA, Croft LB, Benny PS (2003) Evidence that oxytocin is a physiological component of LH regulation in non-pregnant women. *Hum Reprod* 18: 1428–1431
3. Benoussaidh A, Maurin Y, Rampin O (2004) Spinal effects of oxytocin on uterine motility in anesthetized rats. *Am J Physiol Regul Integr Comp Physiol* 287: R446–R453
4. Thornton S, Vatish M, Slater D. (2001) Oxytocin antagonists: clinical and scientific considerations. *Exp Physiol* 86: 297–302
5. Woodcock NA, Taylor CW, Thornton S (2004) Effect of an oxytocin receptor antagonist and rho kinase inhibitor on the Ca⁺⁺-I sensitivity of human myometrium. *Am J Obstet Gynecol* 190: 222–228
6. Caba M, Rovirosa MJ, Silver R (2003) Suckling and genital stroking induces Fos expression in hypothalamic oxytocinergic neurons of rabbit pups. *Brain Res Dev Brain Res* 143: 119–128

7. Gimpl G, Fahrenholz F (2001) The oxytocin receptor system: structure, function, and regulation. *Physiol Rev* 81: 629–683
8. McNeilly AS, Robinson IC, Houston MJ, Howie PW (1983) Release of oxytocin and prolactin in response to suckling. *Br Med J (Clin Res Ed)* 286: 257–259
9. Russell JA, Leng G (1998) Sex, parturition and motherhood without oxytocin? *J Endocrinol* 157: 343–359
10. Argiolas A, Melis MR (2003) The neurophysiology of the sexual cycle. *J Endocrinol Invest* 26 (3 Suppl): 20–22
11. Carmichael MS, Humbert R, Dixen J, Palmisano G, Greenleaf W, Davidson JM (1987) Plasma oxytocin increase in the human sexual response. *J Clin Endocrinol Metab* 64: 27–31
12. Carter CS (1992) Oxytocin and sexual behaviour. *Neurosci Biobehav Rev* 16: 131–144
13. Murphy MR, Checkley SA, Seckl JR, Lightman SL (1990) Naloxone inhibits oxytocin release at orgasm in man. *J Clin Endocrinol Metab* 71: 1056–1058
14. Bulletti C, de Ziegler D (2005) Uterine contractility and embryo implantation. *Curr Opin Obstet Gynecol* 17: 265–276
15. Leyendecker G, Kunz G, Herbertz M, Beil D, Huppert P, Mall G, Kissler S, Noe M, Wildt L (2004) Uterine peristaltic activity and the development of endometriosis. *Ann N Y Acad Sci* 1034: 338–355
16. Kissler S, Siebzehnuebl E, Kohl J, Mueller A, Hamscho N, Gaetje R, Ahr A, Rody A, Kaufmann M (2004) Uterine contractility and directed sperm transport assessed by hysterosalpingoscintigraphy (HSSG) and intrauterine pressure (IUP) measurement. *Acta Obstet Gynecol Scand* 83: 369–374
17. Lyons EA, Taylor PJ, Zheng XH, Ballard G, Levi CS, Kredentser JV (1991) Characterization of subendometrial myometrial contractions throughout the menstrual cycle in normal fertile women. *Fertil Steril* 55: 771–774
18. Fukuda M, Fukuda K (1994) Uterine endometrial cavity movement and cervical mucus. *Hum Reprod* 9: 1013–1016
19. Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G (1996) The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. *Hum Reprod* 11: 627–632
20. Kissler S, Wildt L, Schmiedehausen K, Kohl J, Mueller A, Rody A, Ahr A, Kuwert T, Kaufmann M, Siebzehnuebl E (2004) Predictive value of impaired uterine transport function assessed by negative hysterosalpingoscintigraphy (HSSG). *Eur J Obstet Gynecol Reprod Biol* 113: 204–208
21. Kissler S, Doeinghaus K, Becker W, Wildt L (1995) Hysterosalpingoscintigraphic examination of the fallopian tube: a selective, unilateral transport mechanism. *Contracept Fertil Steril* 23: OC-286
22. Wildt L, Kissler S, Licht P, Becker W (1998) Sperm transport in the human female genital tract and its modulation by oxytocin as assessed by hysterosalpingoscintigraphy, hysteronography, electrohystero-graphy and Doppler sonography. *Hum Reprod Update* 4: 655–666
23. Bulletti C, Jasonni VM, Lubicz S, Flamigni C, Gurpide E (1986) Extracorporeal perfusion of the human uterus. *Am J Obstet Gynecol* 154: 683–8
24. Bulletti C, Jasonni VM, Martinelli G, Covoni E, Tabanelli S, Ciotti PM, Flamigni C (1987) A 48-hour preservation of an isolated human uterus: endometrial responses to sex steroids. *Fertil Steril* 47: 122–9
25. Bulletti C, Jasonni VM, Ciotti PM, Tabanelli S, Naldi S, Flamigni C (1988) Extraction of estrogens by human perfused uterus. Effects of membrane permeability and binding by serum proteins on differential influx into endometrium and myometrium. *Am J Obstet Gynecol* 159: 509–15
26. Bulletti C, Jasonni VM, Tabanelli S, Gianaroli L, Ciotti PM, Ferraretti AP, Flamigni C (1988) Early human pregnancy in vitro utilizing an artificially perfused uterus. *Fertil Steril* 49: 991–996
27. Richter O, Wardelmann E, Schneider C, Kiel R, Wilhelm K, Schmolling J, Kupka M, van der Ven H and Krebs D (2000) Extracorporeal perfusion of human uterus as an experimental model in gynaecology and reproductive medicine. *Hum reprod* 15: 1235–1240
28. Richter ON, Tschubel K, Schmolling J, Kupka M, Ulrich U, Wardelmann E (2003) Immunohistochemical reactivity of myometrial oxytocin receptor in extracorporeally perfused nonpregnant human uteri. *Arch Gynecol Obstet* 269: 16–24
29. Richter ON, Kubler K, Schmolling J, Kupka M, Reinsberg J, Ulrich U, van der Ven H, Wardelmann E, van der Ven K (2004) Oxytocin receptor gene expression of estrogen-stimulated human myometrium in extracorporeally perfused non-pregnant uteri. *Mol Hum Reprod* 10: 339–346
30. Richter ON, Bartz C, Dowaji J, Kupka M, Reinsberg J, Ulrich U, Rath W (2005) Contractile reactivity of human myometrium in isolated non-pregnant uteri. *Hum Reprod* doi:10.1093/humrep/dei295
31. Bulletti C, Prefetto RA, Bazzocchi G, Romero R, Mimmi P, Polli V, Lanfranchi GA, Labate AM, Flamini C (1993) Electromechanical activities of human uteri during extracorporeal perfusion with ovarian steroids. *Hum Reprod* 8: 1558–63
32. Bulletti C, DeZiegler D, Stefanetti M, Cicinelli E, Pelosi E, Flamini C (2001) Endometriosis: absence of recurrence in patients after endometrial ablation. *Hum Record* 16: 2676–9
33. Bulletti C, DeZiegler D, Polli V, Del Ferro E, Palini S, Flamini C (2002) Characteristics of uterine contractility during menses in women with mild to moderate endometriosis. *Fertil Steril* 77: 1156–61
34. Dittrich R, Maltaris T, Mueller A, Dragonas C, Scalera F, Beckmann MW (2003) The extracorporeal perfusion of swine uterus as an experimental model: the effect of oxytocic drugs. *Horm Metab Res* 35: 517–522
35. Maltaris T, Dragonas C, Hoffmann I, Mueller A, Schild RL, Schmidt W, Beckmann MW, Dittrich R (2005) The extracorporeal perfusion of the swine uterus as an experimental model: the effect of tocolytic drugs. *Eur J Obstet Gynecol Reprod Biol* (Epub ahead of print)
36. Maltaris T, Scalera F, Schlembach D, Hoffmann I, Mueller A, Binder H, Goecke T, Hothorn T, Schild RL, Beckmann MW, Dittrich R (2005) Increased uterine arterial pressure and contractility of perfused swine uterus after treatment with serum from pre-eclamptic women and endothelin-1. *Clin Sci (Lond)* 109: 209–215
37. Bulletti C, Jasonni VM, Tabanelli S, Gianaroli L, Ciotti PM, Ferraretti AP, Flamigni C (1988) Early human pregnancy in vitro utilizing an artificially perfused uterus. *Fertil Steril* 49: 991–996
38. Bickers W, Main RJ (1941) Patterns of uterine motility. *J Clin Endocrinology* 1: 992–995
39. Levin RJ (1992) The mechanisms of human female sexual arousal. *Annual Revue of Sex Research* 3: 1–48
40. Eisenbach M (1995) Sperm changes enabling fertilization in mammals. *Cur Opin Endocrinol and Diabetes* 2: 468–475
41. Levin RJ (2002) The physiology of sexual arousal in the human female: a recreational and procreational synthesis. *Archives of Sexual Behavior* 31: 405–411
42. Martinez-Gaudio M, Yoshida T, Bengtsson LP (1973) Propagated and nonpropagated myometrial contractions in normal menstrual cycles. *Am J Obstet Gynecol* 115: 107–111
43. Birnholz JC (1984) Ultrasonic visualization of endometrial movements. *Fertil Steril* 41: 157–158

44. Abramowicz JS, Archer DF (1990) Uterine endometrial peristalsis: a transvaginal ultrasound study. *Fertil Steril* 54: 451–454
45. Kido A, Togashi K, Nakai A, Kataoka ML, Koyama T, Fujii S (2005) Oral contraceptives and uterine peristalsis: evaluation with MRI. *J Magn Reson Imaging* 22: 265–270
46. Mueller A, Siemer J, Maltaris T, Binder H, Kaja H, Beckmann MW, Dittrich R (2005) The imbalance between vasoconstrictors and vasodilators in serum from pre-eclamptic women; results from perfused swine uteri using a complete digital measurement and data recording system. *Med Hypotheses Res* 2: 543-551
47. Lippert TH, Seeger H, Mueck AO (2005) Oxytocin functions outside pregnancy. *Geburtshilfe Frauenheilk* 65: 844–849

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