Physiology of Upward Transport in the Human Female Genital Tract

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ABSTRACT: The uterus and fallopian tubes represent a functionally united peristaltic pump under the endocrine control of ipsilateral ovary. We have examined this function by using hysterosalpingoscintigraphy (HSS), recording of intrauterine pressure, electrohysterography, and Doppler sonography of the fallopian tubes. An uptake of labeled particles into the uterus was observed during the follicular and luteal phases of the cycle after application into the vagina. Transport into the oviducts, however, could only be demonstrated during the follicular phase. Furthermore, the predominant transport was into the tube ipsilateral to the ovary containing the dominant follicle. The pregnancy rate following spontaneous intercourse or insemination was higher in those women in whom ipsilateral transport could be demonstrated. The amount of material transported to the ipsilateral tube was increased after oxytocin administration, as demonstrated by radionuclide imaging and by Doppler sonography following instillation of ultrasound contrast medium. An increase in the basal tone and amplitude of contractions was observed after oxytocin administration. These results support the idea that the uterus and fallopian tubes act as a peristaltic pump, which increases transport of sperm into the oviduct ipsilateral to the ovary bearing the dominant follicle. Oxytocin appears to play a critical role in this peristaltic pump. A failure of the peristaltic mechanism is possibly responsible for infertility. We propose the term tubal transport disorder (TTD) as a nosological entity. Results from HSS could be a useful adjunct for choosing treatment modalities in patients with patent fallopian tubes suffering from

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infertility. These patients may be better served with *in vitro* fertilization (IVF).

KEYWORDS: sperm transport; female genital tract; hysterosalpingoscintigraphy; intrauterine pressure; oxytocin; infertility

INTRODUCTION

One of the critical steps in the process of reproduction is the transport of spermatozoa from the vagina to the pars ampullaris of the fallopian tube. Its successful completion requires a mechanical patency as well as a functional integrity of the uterus and the oviducts.[1,2] The biological significance and pathophysiology of transport function, in contrast to simple mechanical patency of the female genital tract, have also not been completely understood. The procedures used for clinical evaluation of the uterus and oviduct, that is, hysterosalpingography (HSG), hysterosalpingocontrastultrasonography (HyCoSy), and laparoscopy with chromopertubation (LSCP) are based on the infusion of liquid media into the uterus, such as a radiological water-soluble contrast medium, a contrast medium developed for ultrasonography and a solution of methylene-blue during laparoscopy, using pressure to force their passage through the fallopian tubes into the abdominal cavity, and mainly assess mechanical patency.[3–5] Mechanical patency does not necessarily equate with functional integrity. Up to now, development and clinical application of methods for the assessment of functional aspects of the genital tract with regard to transport processes have not been available and thus not examined as possible diagnostic tools. By studying aspects of transport mechanisms in the uterus and the fallopian tubes through the use of hysterosalpingoscintigraphy (HSS), in conjunction with other biophysical and pharmacological interventions, we offer new insights into the pathophysiology of the female reproductive tract. Consequently, we suggest that tubal transport disorders (TTD), which can be diagnosed by HSS, may represent a thus far unrecognized factor in infertility.

METHODS

Patients

We reviewed the results of HSS in more than 1,000 women, ages 20–46, suffering from primary or secondary infertility of various etiologies, who underwent HSS followed by HyCoSy, to evaluate uterine and fallopian tube function. These women also underwent other diagnostic procedures, such as cycle monitoring combining determination of luteinizing hormone (LH), estradiol (E2), and progesterone in serum with sonographic determination of follicular development. Informed consent was obtained from all participants.

Materials

Urinary silastic catheters 6 or 8 charriere for intrauterine application of contrast medium fitted with an inflatable balloon were used (Uromed Kurt Drews GmbH, Oststeinbeck, Germany). We prepared the recording electrodes for electrohysterography using cephalic electrodes from Hewlett Packard Medical Products Group, Waltham MA, USA. Silastic, polyethylene, and teflon tubing was obtained from Reichelt Chemietechnik, Heidelberg, Germany.

Cycle Monitoring

We defined a dominant follicle as a follicle with a diameter of more than 10 mm and determined LH, E2, and progesterone in blood samples collected once daily starting on day 10 of the cycle using commercially available immunoassays (Boehringer Mannheim, Germany). The luteal phase was assessed by progesterone levels taken every 2–5 days during the 2 weeks after the beginning of the LH surge until the onset of menstruation. Ultrasonography was used to monitor follicular development using Siemens Sonoline AC and Siemens Versa Pro ultrasound devices (Siemens AG, Erlangen, Germany), both equipped with 5.0–7.5 MHz vaginal probes.

HSS

HSS was performed in the follicular phase of the cycle in 1,000 patients. Fifteen patients were examined inadvertently during the early- to midluteal phase. The largest follicle was identified by ultrasonography on the day of examination and its localization (left or right ovary) and diameter were determined. Using a catheter we applied 10 ± 2 MBq-TC-99 m labeled macroaggregates of human serum albumin (SolcoMAA, Solco Basel AG, Birsfelden Switzerland) with a size of 5–20 Hm, corresponding roughly to the size of spermatozoa, in a volume of 1–2 mL to the posterior vaginal fornix with the patient in a supine position. Scans with a gamma camera were obtained immediately after application and at various time intervals for up to 4 h, as already described.[6,7] Color printouts of the scans were used for evaluation. A small mark was set on the skin between symphysis pubis and the umbilicus for topographical identification. The results were rated as (a) radioactivity within the cavum uteri, (b) radioactivity within the fallopian tubes, and (c) radioactivity within the abdominal cavity. Combining the examination with the findings obtained by ultrasonography, the results were further classified as ipsilateral when radioactivity concentrated predominantly within the fallopian tube on the side of the dominant follicle, as contralateral when radioactivity was detected predominantly in the tube opposite to the side of the dominant follicle,

as bilateral when activity was found equally distributed within both tubes, and as unilateral when activity was found within one tube only, but no dominant follicle was identified by ultrasound.

Validation of HSS

A bladder catheter was placed into the uterus in 4 patients after the examination was completed and flushed with 3 mL of saline to ascertain that the labeled material had remained in an intrauterine or intratubal position. The amount of radioactivity in the region of the uterus was determined and compared to that in the abdominal cavity by taking an additional scan after flushing. In addition, fluid was collected from the pouch of Douglas in 3 patients who underwent laparoscopy on the HSS day and the radioactivity of the fluid was counted in a well-type gamma counter. The fluid was divided into two aliquots. One aliquot (0.5 mL) was mixed with 3 mL 20% trichloracetic acid. The sample was centrifuged, the supernatant removed, and the radioactivity in the precipitate was counted. The second aliquot was centrifuged, the pellet washed once with saline and counted after recentrifugation for 10 min. Microscopic examination of the pellet was done.

Effects of Oxytocin

The transport of radiolabeled microspheres was used to examine the effects of oxytocin in 50 patients, using serial HSS scans. The first scan was performed immediately after application of the microspheres to the vagina, followed 8–10 min later by a second scan. After intravenous (i.v.) administration of 3 international units (IU) oxytocin (Syntocinon, Sandoz AG, Nürnberg, Germany), two additional scans were taken, one immediately after oxytocin injection and the second scan 8–10 min later. Regions of interest (ROI) were placed for quantitative evaluation on both sides of the uterus in the area of the fallopian tubes and the radioactivity per unit time within these areas was recorded and plotted.

Measurement of Intrauterine Pressure (Hysterotonography)

During the follicular phase of the cycle, the intrauterine pressure was recorded in 25 patients using either a catheter fitted with two Millar-microtip transducers positioned 6 cm apart or with two catheters filled with sterile water, each connected to a Gould–Statham element as pressure recorder. The catheters were made from teflon or polypropylene tubing with an outer diameter of 1 mm and fitted at the tip with a small, inflatable rubber balloon as pressure

sensor (Hugo Sachs Elektronik, March-Hugstetten, Germany). The catheters were placed under ultrasonographic guidance into the uterus with the tip of the first catheter at the fundus (position I), and the tip of the second catheter just behind the internal os (position II). The catheters were either connected with an 8-charriere bladder catheter that could be blocked by an inflatable balloon or held in place by a wire clip attached to the cervix, so that their expulsion could be avoided. Using this multichannel recorder, the differential between the pressure measured at positions I and II (intrauterine pressure) was recorded for 10 to 20 min. Oxytocin was administered either i.v. (3 IU) or as nasal spray (4 IU) and recording continued for another 10 to 20 min. Frequency and amplitude of contractions and the pressure gradients between fundus and cervix uteri were determined using calipers.

Electrohysterography

Two silver electrodes made from a cephalic electrode were used for recording uterine electrical activity in 20 patients. The wires were immersed repeatedly into a solution prepared by mixing 1 mL medical grade silastic adhesive with 5 mL n-Hexane and allowed to dry at room temperature under a light stream of air for insulation. The insulating silastic layer was then removed carefully with a scalpel at a length of 2 mm from the tip of the wires. By placing one electrode into the fundus uteri and fixing the second one at the external os or within the cervix, we could measure electrical potentials continuously and record them with a Biofeedback system (SOM Biofeedback, Murrhardt, Germany) connected to a computer. A computer program adapted from a program for detection of pulses of hormones in plasma[8] identified the amplitude and frequency of spikes and calculated the variability from point to point.

Doppler Ultrasonography of the Fallopian Tubes

Performing Doppler ultrasonography in 60 patients who underwent HyCoSy was used to determine flow through the fallopian tubes. We infused contrast medium (Echovist 300, Schering AG, Berlin, Germany) into the uterus via a catheter until the uterine cavity and the fallopian tubes could be visualized either by vaginal or by abdominal ultrasonography. After removal of the catheter, a pulsed Doppler beam was directed to the cavum uteri and the fallopian tubes. The ultrasound probe was held in place by a clamp fitted to a colposcope holder. Oxytocin was administered i.v. or intranasally at doses of 4 and 3 IU per application, respectively, after 2–5 min and the recording of Doppler signals was continued. A video printer was used during the recording periods. An increase to at least 10 cm/sec for a duration of at least 1 sec was defined as a signal. Frequency and intensity of the signals on the printout were determined using mechanical calipers.

Measurement of Ciliary Beat Frequency

Using a photoelectric technique and fast Fourier transform analysis, we determined the baseline ciliary beat frequency (CBF) of fimbria under standardized temperature conditions. Fimbrial portions of fallopian tubes were collected from 21 patients undergoing post partum sterilization, after obtaining written informed consent and local ethical committee approval. All study subjects had regular menstrual cycles before gravidity and no subject had used hormonal medications during pregnancy. Normal appearing, representative sections of fimbrial tissues, 0.5–1 cm in length, of both fallopian tubes of each subject were rinsed several times to remove all visible evidence of blood. Changes in CBF were documented by ROI measures for temperatures ranging from 37–39°C.

Clinical Evaluation of Tubal Patency

The mechanical tubal patency is defined as the observation of flow into the abdomen revealed by one of the following methods: HSG, HyCoSy, or LSCP. HSG was performed with a Schultze apparatus applied to the cervix for instillation of a radiological water-soluble contrast medium into the uterus (Isovist 300, Schering AG, Berlin, Germany). During HyCoSy a bladder catheter (Kinder- Ballon-Katheter 6 charriere, Uromed) was placed into the uterus and blocked; 2–4 mL of contrast medium developed for ultrasonography (Echovist 300, Schering AG, Berlin, Germany) was infused via the catheter into the uterus. The flow into the uterine cavity and the fallopian tubes was monitored by vaginal ultrasonography. Chromopertubation during laparoscopy was performed by placing a portio adapter into the uterus and infusing a solution of methylene-blue, with visualization of contrast escaping the fimbria as evidence of patency.

Statistical Analysis

The SPSS software package versions 6.1.3–11.00 were used for statistical analysis. Multiple data sets were analyzed by analysis of variance (ANOVA) followed by the Newman–Keuls test for comparing means. The level of significance was set as $P \leq 0.05$. Chi-squared analysis was used for testing distributions. Paired *t*-test was used when the effects of treatment were compared.[9]

RESULTS

Rapid transport of the microspheres from the vagina into the uterine cavity was confirmed by the detection of labeled particles in the uterus at the time of

the first HSS scan, as early as 2 min after intravaginal application. Uptake into the uterus was observed during the follicular as well as during the luteal phases of the cycle in every patient examined. Radioactivity entered the fallopian tubes either on both sides (15%) or on only one side (64%) in 79% of the patients studied during the follicular phase. In the remaining patients, radioactivity was detected only in the uterine cavity and did not migrate into the fallopian tubes. FIGURE 1 shows typical examples of the scans. Significant radioactivity entering the pelvis was observed in only 6% of the patients.

The ascension of radioactive particles into the uterus in the 15 patients examined during the luteal phase appeared to be indistinguishable from that observed during the follicular phase. However, we did not observe transport into the oviducts in any of the patients examined during the luteal phase. In addition, in these 10 women, we observed a qualitatively different pattern of distribution of radioactivity within the uterus compared to that observed during the follicular phase of the cycle. A rather broad area of radioactivity was observed during the luteal phase giving the impression of a large cavum uteri, while during the follicular phase, the area of maximal activity had an elongated shape.

Radioactivity from the uterine cavity and the oviducts was completely dispersed by flushing the uterus with a small volume of saline (~ 3 mL). In addition, more than 90% of radioactivity in the fluid collected from the cul de sac in 3 patients who underwent laparoscopy was found in the pellet after centrifugation and could be precipitated by trichloracetic acid, indicating that most of the radioactivity was still protein bound.

FIGURE 2 shows the relationship between ipsilateral and bilateral entry of radioactivity into the fallopian tubes and the size of the dominant follicle. The frequency of ipsilateral transport of activity into the oviduct was found to increase from 10% to 75% with increasing diameter of the leading follicle,

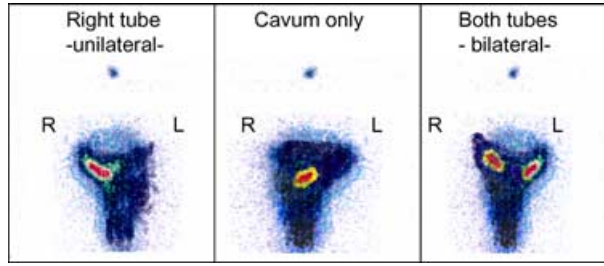

FIGURE 1. Typical examples of scans taken 10–20 min after application of 10–12 MBq 99mTc labeled microspheres to the posterior vaginal fornix, demonstrating (from left to right) uptake into the uterus and unilateral transport to the right fallopian tube (**A**), uptake into the uterus only (**B**), and bilateral transport into the oviducts (**C**). A marker is placed at half distance between the symphysis and umbilicus (reprinted from Wildt *et al*.[27] with permission).

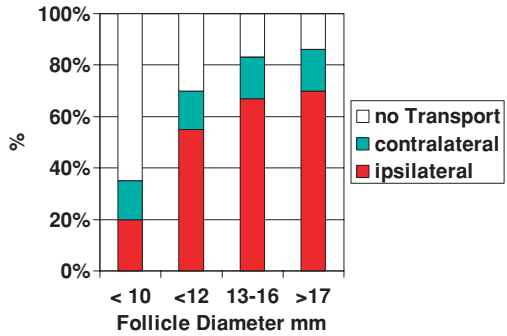

FIGURE 2. Lateralization of transport of labeled microspheres and size of the leading follicle. With increasing diameter of the dominant follicle, the proportion of patients exhibiting ipsilateral transport to the oviduct leading to the dominant follicle did increase progressively. The proportion of patients who had ipsilateral transport was higher in those who became pregnant after timed intercourse or intrauterine insemination than in those who did not conceive after this treatment (Treatment duration lasting up to 6 cycles). Up to a follicle size of 13 mm, ipsilateral transport could be diagnosed only in retrospect, at the time when a dominant follicle appeared on the side where radioactivity was concentrated.

when all patients were included in the analysis. The percentage of patients with ipsilateral transport was higher and increased from 25% to 95%, when only those patients were considered who later became pregnant either spontaneously or after intrauterine insemination.

TABLE 1 shows the relationship between the outcome of treatment of infertility and the asymmetrical distribution of radioactivity. The combined pregnancy rate for spontaneous pregnancies (Sp) or pregnancies following intrauterine insemination (IUI) in women exhibiting ipsilateral transport was 21.7%; when no entry of radioactivity into the tubes was found, the pregnancy rate was only 2% ($P < 0.05$). In contrast, no significant difference in pregnancy rate (22.7% vs. 24.5%, respectively) could be observed between both groups of patients who underwent *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

The effects of oxytocin administration on transport of radioactivity are shown in FIGURES 3 AND 4. After oxytocin administration, radioactivity within

TABLE 1. Relationship between the outcome of treatment for infertility and the symmetrical distribution of radioactivity

	Ipsilateral Transport	No Transport
Pregnant (Sp*+ IUI)	78/360 (21.7 %)	4/200 (2%)
Pregnant ** (IVF+ICSI)	25/110 (22.7%)	48/196 (24.5%)

*includes pregnancies after normal and timed intercourse.
**includes pregnancies after transfer of cryopreserved pronucleus cells.

the ROI on the ipsilateral side immediately increased, suggesting an increase in the amount of particles transported as a consequence of the administration of the peptide, as shown in FIGURE 3. Radioactivity on the contralateral side, in contrast, did not exhibit dramatic changes. FIGURE 4 summarizes the data for all 50 patients studied. During the luteal phase, oxytocin had no effect on the distribution of radioactivity within the uterus.

Doppler ultrasonography of the uterus and the oviduct filled with contrast medium resulted in eddy formations, indicative of turbulent rather than laminar flow within the tubes. Oxytocin administration resulted in an increase of turbulent flow, as shown in FIGURE 5, but only within the oviduct on the side of the dominant follicle. Only few signals could be detected on the contralateral side before and after the administration of oxytocin.

FIGURE 6 shows the results of the recording of the intrauterine pressure during the follicular phase of the cycle before and after oxytocin administration. Basal pressure increased significantly ($P < 0.05$) immediately following the administration of oxytocin.

FIGURE 7 shows the results of the recording of the CBF under a constant physiological temperature of 37°C. The mean (± SD) baseline in tubal explants

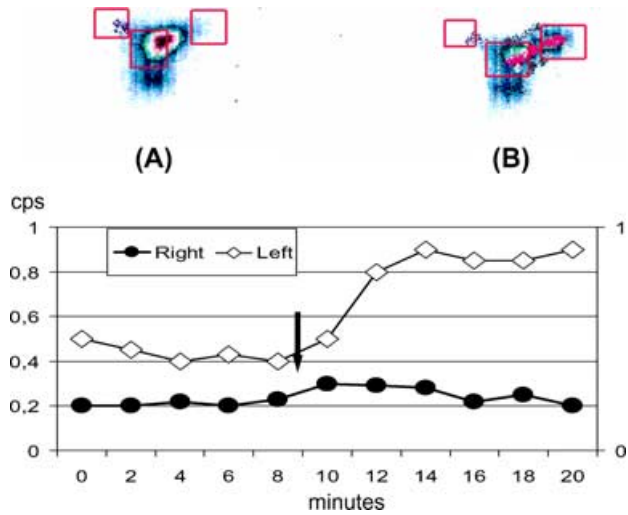

FIGURE 3. Intravenous (i.v.) administration of oxytocin (3 IU) in a patient during HSS. The upper panel (**A** and **B**) shows two scans taken 10 min apart, with the regions of interest (ROI) depicted as boxes over the cavum and the left and right oviducts, respectively. The lower panel shows radioactivity measured within the ROIs over the left and right oviducts and expressed as counts per second. The dominant follicle in this patient was located in the left ovary. Activity on the left side is higher than on the right side. The arrow marks the time when oxytocin was administered; this was followed by an increase of radioactivity found within the ROI on the left side, indicating increased transport into the left oviduct (reprinted from Wildt *et al.*[27] with permission).

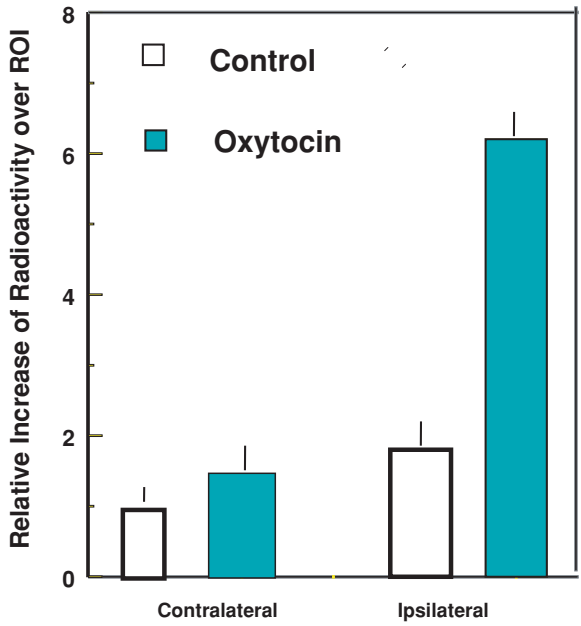

FIGURE 4. Relative increase of the radioactivity detected within the ROI placed over uterus and the fallopian tube leading to the dominant follicle. There is a significant ($P \leq 0.05$) increase in radioactivity immediately after oxytocin administration on the dominant, but not at the contralateral side. Data represent mean ± SD of 50 observations (reprinted from Wildt *et al.*[27] with permission).

of the study population was 7.5 ± 0.5 Hz. A significant increase of CBF of 20% (9.5 ± 0.5 Hz) ($P < 0.05$) was recorded after the temperature increased from 37°C to 39°C.

DISCUSSION

Male germ cells have to migrate from the posterior vaginal fornix to the pars ampullaris of the fallopian tubes to fertilize an oocyte; the fertilized oocyte then has to be transported to the uterine cavity for implantation. The mechanisms and timing of this bidirectional travel are not completely understood. We studied the migration of radiolabeled immotile aggregates of serum albumin, used as surrogates for spermatozoa, from the vagina through the genital tract and explored some of the factors affecting this migration. We provide evidence that upstream transport in the genital tract may be composed of two components: a rapid uptake by the uterus from the vagina and a directed transport from the uterus to the oviduct toward the ovary bearing the dominant follicle. The former is observed during the follicular and luteal phase of the cycle, while

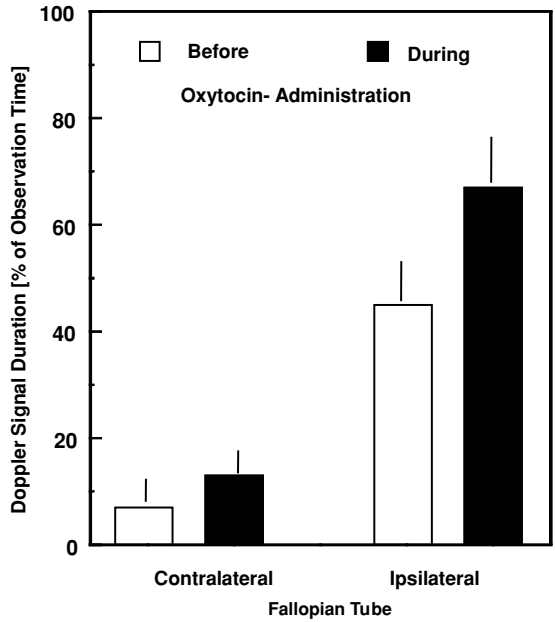

FIGURE 5. Doppler ultrasonography of the left and right fallopian tubes following instillation of echogenic contrast medium before and after oxytocin administration, demonstrating a significant increase ($P \leq 0.05$) in signal density and frequency after administration of the hormone. Data represent mean ± SD of 30 observations (reprinted from Wildt *et al.*[27] with permission).

the latter is restricted to the follicular and preovulatory phase, becoming more prominent when the size of the leading follicle increases. Therefore, we believe that the ovary bearing the dominant follicle controls this directed transport.

All examined patients exhibited an uptake of the radiolabeled aggregates by the uterus. This is an indication that this part of the transport mechanism is rather stable and that inhibition of sperm uptake does not represent a major factor in infertility. The observation of this uptake into the uterus during the luteal phase of the cycle was rather unexpected because of the hypothesis that the cervical mucus becomes impenetrable for spermatozoa under the influence of elevated progesterone serum levels. Spermatozoa have previously been shown to be immotile in luteal phase mucus *in vivo* and *in vitro*, resulting in a failure to penetrate cervical mucus *in vitro* experiments.[10–13] Our results may indicate that this does not necessarily affect that passive transport of spermatozoa, which may not be blocked during the luteal phase. Similar numbers of motile spermatozoa are found within the oviduct during the luteal as in the early- to midfollicular phase of the cycle, as previously reported by studies that examined the presence of spermatozoa in different compartments of the genital tract after intercourse. Nevertheless, the highest number of spermatozoa

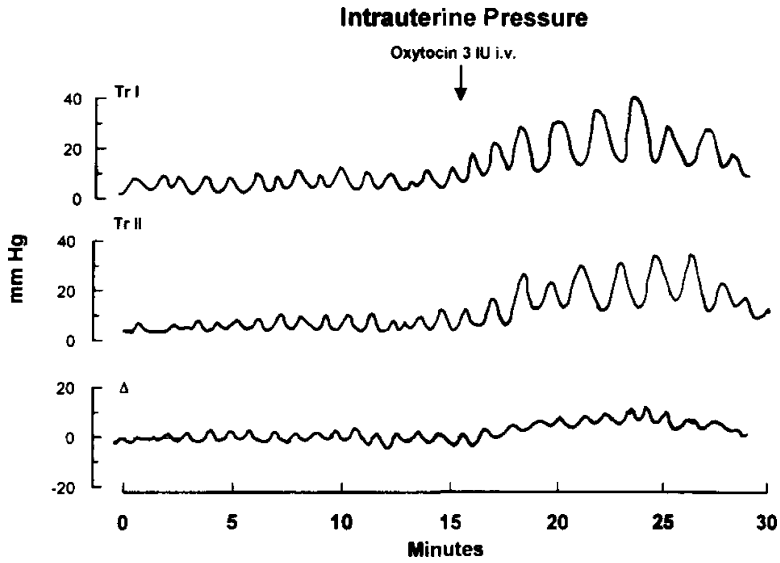

FIGURE 6. Intrauterine pressure recorded during the follicular phase of the cycle before and after the i.v. administration of 3 IU oxytocin. Transducer I (TrI) was placed in the fundal part (**A**), transducer II (TrII) near the internal cervical os (**B**). The arithmetic difference between pressure recorded in position II and the pressure recorded in position I is plotted in the lowest panel (**C**). Note the increase in basal tonus and the increase of the pressure difference between the two recording sites after oxytocin administration. The effect of oxytocin lasted for 20–40 min (reprinted from Wildt *et al*., 1998[27] with permission).

can be detected in the fallopian tube during the preovulatory phase.[10–14] With regard to sperm transport, our interpretation of the results of HSS is based on the assumptions that the properties of the labeled material used for examination are similar to those of human spermatozoa and that there is no separation of label from the carrier *in vivo*. Various radiolabeled compounds have been used the past 30 years for radionuclide imaging of the female genital tract, including aggregates of human albumin, radioactive inert gases, and labeled spermatozoa.[6,15–22] In this study, human serum albumin macroaggregates with Tc-99m attached to the protein by noncovalent binding were used as surrogates for spermatozoa. We feel that we can adequately confirm that the radioactivity was protein-bound because: (1) we observed the disappearance of the radioactivity from the uterus after flushing with saline and (2) the radioactivity collected from the cul de sac at laparoscopy could be precipitated completely by acid and still could be centrifuged down at low speed 4–7 h after application excluding uptake by the lymphatic system.

Although HSS has not been widely used, it is a technically very simple procedure with little discomfort to the patient, in contrast to HSG. There is an apparent discrepancy between the results of HSS and those obtained with HSG

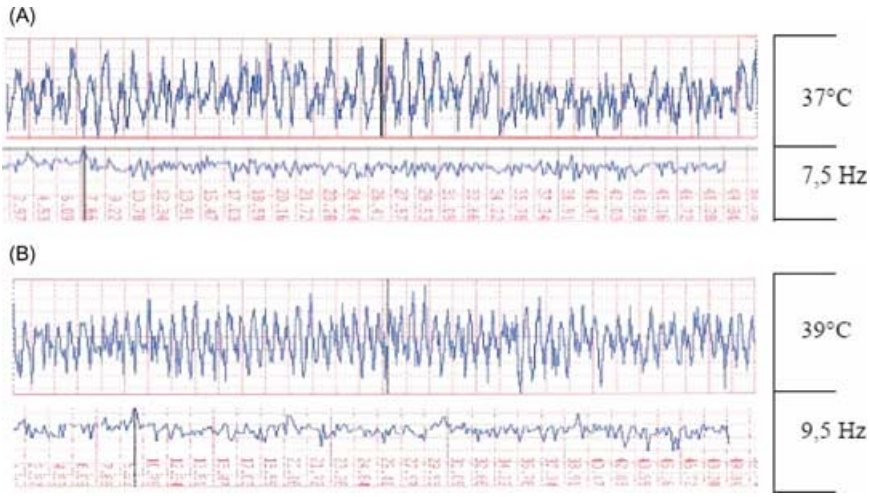

FIGURE 7. Ciliary beat frequency (CBF) is a local phenomenon in fimbrial cilia of human oviducts. Under physiological temperature conditions until 37°C, CBF is 7.5Hz ± 0.5Hz (**A**). As temperature increased to 39°C, CBF increased exponentially up to 20% (9.5 ± 0.5Hz, (**B**). A postovulatory increase of CBF in local areas of fimbrial cilia cells of the ipsilateral tube may guarantee the pickup of the oocyte–cumulus complex into the tube.

or laparoscopy; in the majority of patients with proven patency of both fallopian tubes only one oviduct could be visualized by HSS. The transport of the radiolabeled microspheres is physiologically restricted to the oviduct leading to the ovary bearing the dominant follicle while the contralateral fallopian tube appears to be functionally closed, as it is observed by a detailed analysis of the results of HSS and their correlation with the results of ultrasonography and determination of endocrine parameters for follicular growth.[23–26] Our present study demonstrates that ipsilateral transport, as first shown by our group in 1992,[23] is a reflection of the physiological function of the uterus and the oviduct and not the consequence of tubal pathology or an artifact of the method. This demonstration is supported by the observation that the pregnancy rate after normal intercourse or intrauterine insemination was significantly higher in patients exhibiting ipsilateral transport than in those who did not.

Our results also imply that failure of transport in patients with otherwise mechanically patent fallopian tubes, may be considered an etiology of infertility. Most of the patients examined in this study would have been diagnosed as suffering from idiopathic infertility. We proposed the concept of TTD as a more adequate description of the condition of these patients.[27] The results of HSS may provide criteria for the choice of the adequate therapy in such women, since pregnancy rates in patients with TTD, which are extremely low following insemination or timed intercourse, can be increased substantially by *in vitro* fertilization.

The ovary bearing the dominant follicle appears to control the transport from the uterus to the oviduct. The proportion of patients exhibiting ipsilateral transport increased with the size of the dominant follicle, reaching up to 90% of those patients who became pregnant when the follicle diameter was 19 mm or more. The forces that are driving transport and the mechanisms directing this process need to be defined. Since the particles used for HSS are protein aggregates devoid of motility, motility of the spermatozoa can be excluded. Movements of the ciliae within the oviduct do not seem to be a major factor in rapid transport, since the beat of ciliae is directed from the ampulla to the uterus (the opposite direction), and women with Kartagener Syndrome, that is, congenital absence of ciliae, have no difficulties in becoming pregnant.[1,28–31] It is also unlikely that capillary forces generated within the mucus and a difference in hydrostatic pressure between vagina and peritoneal cavity account for the immediate uptake from the vagina and the directed transport.[32] Peristaltic contractions of the uterus and of the muscular layers of the fallopian tubes therefore represent the most likely candidates responsible for the rapid transport phenomena. Using direct measurement of intrauterine pressure or vaginal ultrasonography combined with videocinematography during the follicular phase of the cycle, peristaltic contractions of the nonpregnant uterus have been described in women during the normal menstrual cycle as well as in women suffering from primary dysmenorrhea or in women with endometriosis.[33–37] The contractions seem to occur with a frequency of 2–5 per min and to exhibit a characteristic pattern of propagation in healthy women, depending on the phase of the menstrual cycle. While a cervicofundal propagation of peristaltic waves was found during the preovulatory phase of the cycle, a fundocervical direction predominated in the early follicular phase.

The strong positive correlation between the temperature and the oocyte pick-up rate in the animaloviductal infundibulum is demonstrated by a linear regression.[38] Preovulatory temperature differences between the ampullary and isthmic portions of a single tube have been previously reported and thought to primarily reflect the extent and activity of the vascular and lymphatic beds in the oviduct tissues.[39–41] We found periovulatory temperature differences of up to 1.5 °C between the two oviducts measured *in vivo* during tubal catheterization in a small group of patients, temperature being higher within the oviduct leading to the ovary bearing the dominant follicle (Wildt *et al*. unpublished) . Furthermore, we found an exponential increase in CBF in the range of physiological temperature. This is in accordance with the report of a significantly higher temperature in the ipsilateral tube corresponding to the dominant follicle compared to the contralateral side in human oviducts.[42] Our data suggest that this difference in periovulatory temperature between the two fimbriae may be responsible for the increased CBF on the side ipsilateral to the dominant follicle, underlining the concept of the uterus consisting of two functionally different components.

A number of hormones and paracrine mediators, such as prostaglandins, vasopressin, oxytocin, and various peptides can induce uterine contractions.[43–46] The administration of oxytocin during HSS was followed by a five- to sevenfold increase in the radioactivity detected in the oviduct ipsilateral to the dominant follicle; in addition, systemic administration of oxytocin increased the amplitude of contractions and reversed the pressure gradient from a fundocervical to a cervicofundal direction. Oxytocin is known to play an important role in eliciting contractions of the pregnant and nonpregnant uterus, while oxytocin receptors have been demonstrated in the nonpregnant uterus of human females and laboratory animals.[43,47–50] Following vaginal distension and cervical stimulation during intercourse, oxytocin is released from the posterior lobe of the pituitary in response to tactile as well as emotional stimuli.[32,51–55] Synthesis of oxytocin has also been demonstrated within the endometrium and the ovary, respectively.[50,56–59] Knaus demonstrated that injections of posterior pituitary extract containing oxytocin promptly induced contractions of the nonpregnant human uterus during the follicular phase, but not after ovulation.[60] Our results show a striking effect of oxytocin on uterine transport mechanisms and are in agreement with the early observations of Knaus, demonstrating the absence of directed transport during the luteal phase.

The electrical activity as a response to the oxytocin administration corresponded to the increase of intrauterine pressure. In most instances, no direct relationship between contractions and electrical activity was found. Further studies are necessary to explore the correlation between electrical activity and intrauterine pressure and to examine the validity of recording electrical potentials for the assessment of uterine contractions.[61,62] The Doppler ultrasonography after administration of ultrasound contrast medium supports the observation of ipsilateral transport into and within the oviduct during scintigraphy. An increase in turbulent flow within the fallopian tube is indicated by an increase in signal density that was consistently observed immediately after oxytocin administration, either i.v. or intranasally. The increase of flow could only be detected within the oviduct leading to the dominant follicle, which shows that transport occurred predominantly in this direction.[27,63]

Although the overall increase in transport may be explained by the stimulatory action of oxytocin on myometrial contractions, additional mechanisms acting at the levels of uterus and oviduct, such as asymmetric distribution of oxytocin receptors or changes in the resistance of the oviducts caused by the activation or relaxation of smooth muscle cells at the uterotubal junction, are required to account for the unilateral transport. This question cannot be answered by the present studies. Therefore, we propose the following hypothesis, schematically depicted in FIGURE 8: (1) The fallopian tubes are functionally closed in the absence of ovarian hormones. (2) Hormones that cause relaxation of smooth muscle cells are produced by the ovary bearing the dominant follicle. (3) Unilateral transport is to be regarded as the consequence of active relaxation of the myometrium at the side of the ovary that is bearing the

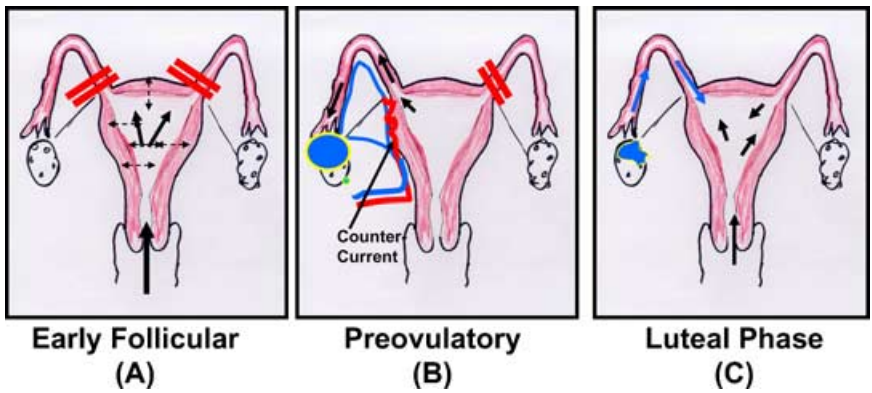

FIGURE 8. Schematic representation of the model of directed transport. During the early follicular phase (**A**) both fallopian tubes are functionally closed, transport occurs from the vagina to the uterine cavity. Contractions of the myometrium, indicated by the broken arrows, which are followed by relaxation, cause a negative pressure within the uterus when compared to the vagina. (**B**) The dominant follicle has been selected. Concentrations of progesterone, produced by the dominant follicle, are elevated at the uterotubal junction due to a countercurrent system indicated by the arrows, causing relaxation of the musculature. Since the contralateral side remains functionally closed, transport is directed into the fallopian tube at the side of the dominant follicle. (**C**) Demonstrates transport during the luteal phase of the cycle. Uptake into the uterus is not impaired, but transport into the fallopian tubes appears to be completely blocked. Transport of the fertilized oocyte is depicted by the arrows within the right fallopian tube, however, the mechanisms governing embryo transport remain to be delucidated.

dominant follicle rather than the induction of a contraction at the contralateral side.

Progesterone can also induce relaxation of the myometrium. The preovulatory follicle produces progesterone in increasing amounts. In addition, progesterone concentrations in the venous effluent from the ovary bearing the dominant follicle are higher than those from the contralateral ovary several days before ovulation.[64,65] Progesterone could be delivered to the area of the uterotubal junction through the arteriovenous countercurrent exchange system that has been identified between the ovary and the uterus.[66–70]

In conclusion, our data demonstrate that the uterus and fallopian tubes seem to act as a functional unit and peristaltic pump that provides the pressure gradients necessary to transport spermatozoa from the vagina to the fallopian tubes. Secretory products originating from the ovary bearing the dominant follicle allow further transport to the ampullary part of the tube on the side of the follicle destined to ovulate, inducing the active relaxation of a functional sphincter mechanism located in the area of the uterotubal junction, while the contralateral oviduct remains functionally closed. Consequently, the probability for fertilization is increased by the maximized number of spermatozoa at

the site where the oocyte is released. Oxytocin contributes to the control of this process by activating pump mechanisms via contraction of uterine smooth muscles. Disturbance of these mechanisms interferes with tubal transport, causing infertility, even in the presence of mechanically open fallopian tubes. HSS appears to be a suitable method to diagnose this TTD.

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