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New Hypotheses

Transvaginal progesterone: evidence for a new functional 'portal system' flowing from the vagina to the uterus

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The results of many recent experimental and clinical studies support the hypothesis that progesterone administered vaginally is distributed selectively to the uterus where tissue concentrations and effects exceed expectations. This phenomenon has multiple clinical implications in several fields of gynaecological endocrinology, notably in assisted reproductive treatments and new forms of hormone replacement therapy. Yet, the actual mechanisms by which vaginal administration of progesterone can induce higher concentrations in the uterus, despite low concentrations in the systemic circulation, remain obscure and most puzzling to many gynaecologists. This review aims to muster ideas and propose different mechanisms to explain the observed phenomenon. In particular, we will summarize data that support the various putative modes of transport including, direct diffusion through tissue, intracervical aspiration, absorption into the venous or lymphatic circulatory systems and countercurrent vascular exchange with diffusion from utero-vaginal veins/lymph vessels to arteries. All these mechanisms may concur to various extents to the uterine specificity of vaginal progesterone.

Key words: endometrium/selective progesterone distribution/vaginal portal system/vaginal progesterone

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Introduction

Most endocrinologists were thought to believe that hormonal blood concentrations were all that count because they represent the signal controlling the effects on target organ(s). The mold from which this thinking evolved is the world of blood sugar homeostasis. Having been the first endocrine mechanism to be elucidated, the hormonal control of blood sugar naturally served as a cradle for all the future domains of 'new-born endocrinology'. The original paradigm was straightforward. Insulin concentrations control glycaemia following a simple equation: a little more or less of insulin present in the blood results in predictable changes in blood glucose. Hence, it could be rightly said that insulin truly controls blood glucose. Later, other homeostatic systems have been unearthed that fitted nicely within this original model (e.g. the hormonal control of calcaemia).

Yet we now realize that different modes of endocrine interactions can also prevail, particularly between reproductive hormones and their target organs. Specifically, we recognized that relationships between hormone concentrations and effects

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are far more complex than originally thought. In this respect, reproductive endocrinology has reserved us a few surprises. First, it has become evident that at each stage of this discipline (pituitary, ovary or uterus), target organs mainly receive 'permissive' rather than 'controlling' orders from their dedicated hormone(s) (de Ziegler, 1995). This already shattered a few existing premises and dogmas on functional links between hormonal concentrations and effects on end-organs. A second—and even more unexpected—form of discordance has been recently unveiled between the concentrations of hormones and the effects in the case of their vaginal administration. With vaginal treatments, it has now become apparent that the low concentrations of plasma progesterone achieved contrast with the high endometrial efficacy observed (Miles *et al*., 1994; Fanchin *et al*., 1997). This latter finding was recently attributed to a previously unknown direct transport phenomenon involving the vascular system (Cicinelli *et al*., 1998). Uncovered by studying the vaginal administration of progesterone, this direct transport phenomenon is likely to have physiological implications that reach far beyond the mere issues pertinent to drug delivery.

Today, a wealth of data suggest that the endometrial tropism of vaginal progesterone results from a fraction of progesterone administered vaginally travelling directly from the vagina to the uterus. There, it enhances tissue concentrations achieved in this organ. This newly minted local vagina-to-uterus 'portal system' or 'first uterine pass effect' brings new understandings, but also raises new questions pertinent to reproductive physiology. The experimental basis supporting the existence of this local 'portal system' running from the vagina to the uterus, its putative underlying mechanism(s) and practical implications in other reproductive endocrine interactions, are the topics of the present review.

We have divided the arguments into three sections. First, a survey of the evidence that supports the view that vaginal administration of progesterone results in high endometrial efficacy despite relatively low progesterone concentrations in peripheral blood. Second, a summary of the experimental data confirming that, from a functional point of view, a direct local 'portal' transport system exists. Third, a review of the putative mechanisms of action underlying this phenomenon. Emphasis will be put on the description of experimental data supporting the involvement of an original 'countercurrent' vascular exchange mechanism with vein to artery diffusion for this local transport. We will stress also the potential clinical implications of this newly uncovered phenomenon beyond the simple issues linked to exogenous progesterone administration.

In order to avoid any issues of conflict of interest, the position of Dr de Ziegler within Columbia Laboratories is clearly stated in the authorship details. Columbia Laboratories is the developer of Crinone, but not its distributor (Wyeth-Ayerst Laboratories, Radnor, PA, USA).

Physiological progesterone replacement

Progesterone, the native hormone produced by the corpus luteum during the luteal phase of the menstrual cycle, is the unique option when we seek 'physiological' hormonal replacement therapy (HRT). This is particularly the case for women who attempt to become (or are already) pregnant through assisted reproductive techniques. There are also other specific circumstances in gynaecology where physiological replacement of progesterone is preferred. In recipients of donor egg in-vitro fertilization (IVF), vaginal progesterone has been shown to be as effective as intramuscular (im) injections for priming endometrial receptivity and sustaining pregnancy (Gibbons *et al*., 1998). Vaginal progesterone has also been used successfully as part of HRT for various conditions (Warren *et al*., 1999), including for menopause (de Ziegler *et al*., 1999). In all these cases natural progesterone is absolutely indicated (IVF) or preferred (HRT) because of possible adverse consequences or subjective side effects of synthetic progestins. Yet, because of the lack of an appropriate pharmacological preparation, physiological progesterone replacement has remained limited until now. Oral progesterone formulations exist, but these have very low bioavailability (<10%) because of rapid intestinal and liver metabolism. After oral administration of progesterone, low circulating concentrations of progesterone contrast with the high concentrations of progesterone metabolites, notably 5α-reduced metabolites which are known sources of neuropsychological side effects (Nahoul *et al*., 1987; Arafat *et al*., 1988). This hormonal profile with minimally elevated progesterone explains the observation that oral progesterone fails to induce predecidual changes in the endometrium (Bourgain *et al*., 1990) and luteal support in IVF (Devroey *et al*., 1989).

Daily i.m. injections are effective notably in infertility, but are painful and not conceivable for long-term treatments. Vaginal administration, however, has been found effective and well accepted by women because of the limited side effects (Bourgain *et al*., 1990; Gibbons *et al*., 1998). Logically therefore, the vaginal route has gained credit particularly for short-term administration such as required in infertility treatments. In many countries, vaginal progesterone has become the primary mode of luteal support in IVF and other related assisted reproduction treatments (Bourgain *et al*., 1990; Artini *et al*., 1995). It has been shown however, that vaginal absorption of progesterone may be influenced by the degree of vaginal mucosa oestrogenization (Villanueva *et al*., 1981), as well as by the characteristics of the formulation used (Price *et al*., 1983; Fulper *et al*., 1987; Kimzey *et al*., 1991). Moreover, until the recent development of sustained-release forms (Fanchin *et al*., 1997), multiple daily administrations were needed which limited the possibility of long-term treatment. Except for the recently developed sustained-release

vaginal gel of progesterone, none of the preparations used was either of pharmaceutical grade (vaginal suppositories are not) or originally designed for vaginal use (oral micronized progesterone capsules were re-directed to be used vaginally).

The first uterine pass effect

In the past few years there has been renewed interest in the vaginal route, particularly for administering progesterone, with growing evidence supporting a preferential or selective distribution to the uterus. This phenomenon has been called the 'first uterine pass effect' (de Ziegler, 1995). The basis for the hypothesis of this local transport system is rooted in the characteristic dissociation between serum progesterone concentration and endometrial histology. While the former is often low or 'sub-physiological', endometrial effects show in most cases clear and complete secretory changes. This discrepancy was stressed to a maximum when a sustained-release vaginal gel of progesterone, Crinone (Wyeth-Ayerst Laboratories, Radnor, PA, USA), was used at half the recommended dose and frequency of administration (45 mg every 48 h). This resulted in frankly low serum progesterone concentrations (in the luteal phase defect range), but did not hamper endometrial efficacy (Fanchin *et al*., 1997). On the contrary, repeated nasal administration of progesterone that resulted in serum progesterone concentrations in the same range as those observed after vaginal administration induced only partial secretory transformation of the endometrium (endometrial glands only) (Cicinelli *et al*., 1993). That similar systemic concentrations of progesterone induced different endometrial responses has been a keystone in the hypothesis that vaginal administration results in selective distribution to the uterus.

In 1994, Miles and co-workers provided direct demonstration of selective distribution of progesterone from the vagina to the uterus. When comparing vaginal and i.m. progesterone, these authors observed that vaginal administration led to lower serum progesterone concentrations and yet higher tissue concentrations of progesterone in the endometrium as compared with measurements made after i.m. administration (Miles *et al*., 1994). Results of recent clinical studies are also in agreement with the hypothesis of a preferential distribution to the uterus of progesterone administered vaginally. Gibbons and co-workers randomized women undergoing a donor egg programme into two groups receiving either the sustained-release gel of progesterone 8% (90 mg of micronized progesterone per gel application, twice daily from the evening of cycle day 14 to day 27) or i.m. progesterone (100 mg from cycle days 15 to 27) replacement (Gibbons *et al*., 1998). They reported higher mean serum progesterone concentrations in the i.m. treatment group as compared with women in the Crinone group, yet despite this, endometrial histology was 'in phase' in all subjects of both groups. Moreover, ongoing pregnancy and implantation rates in subjects receiving Crinone in preparation for their actual embryo transfer were not different from those seen in women receiving i.m. progesterone. These authors concluded logically that vaginal progesterone replacement was as effective as i.m. progesterone in producing clinical and ongoing pregnancies within their donor egg programme (Gibbons *et al*., 1998).

Mechanisms of action explaining the uterine tropism of vaginal progesterone

Little is known about the routes and kinetics governing the direct transport of hormones from the vagina to uterus. Theoretically, at least four different mechanisms can be contemplated as possibly explaining this unexpected phenomenon: (i) direct (passive) diffusion through tissues; (ii) passage through the cervical lumen from the vagina to the uterus; (iii) transport via the venous or lymphatic circulatory systems; and (iv) countercurrent vascular exchange with diffusion between utero-vaginal veins and/or lymph vessels and arteries.

In the following pages we briefly review the experimental and clinical data that support these various mechanisms each as a putative explanation for the selective distribution of progesterone to the uterus after vaginal administration.

Direct (passive) diffusion through tissues

Direct vagina-to-uterus diffusion through tissues has been demonstrated in humans in an in-vitro extracorporeal perfusion non-recycling system (Bulletti *et al*., 1997). A mixture of tritiated ([^{3}H]) and unlabelled progesterone was applied to the cuff of vaginal tissue remaining attached to the cervix after hysterectomy. At the end of the perfusion period (up to 12 h), ^{3}H and ^{14}C radioactivity were measured in samples of uterine tissue. Tritiated water and [^{14}C]dextran were tested to determine the extent of non-specific vagina-to-uterus transport (leaks). Finally, sections of uterine tissue exposed only to [^{3}H]progesterone were prepared for autoradiography. The uterus was perfused with an open system that avoids the possibility of recirculation. Results are illustrated in Figure 1. Absorption in the uterine vein occurred early, peaking 1–2 h after the placement of [^{3}H]progesterone. In contrast, uterine concentrations of progesterone peaked 5 h after vaginal administration when it reached 265 ± 64 and 299 ± 87 ng/100 mg of endometrial and myometrial tissue respectively. Endometrial extraction of progesterone was higher when experiments were performed on uteri obtained during the luteal phase (280 ± 156 ng/100 mg of endometrial tissue) as compared with tissue removed during the proliferative phase of the menstrual cycle (74 ± 28 ng/100 mg of endometrial tissue). Because of the open perfusion system used in this model,

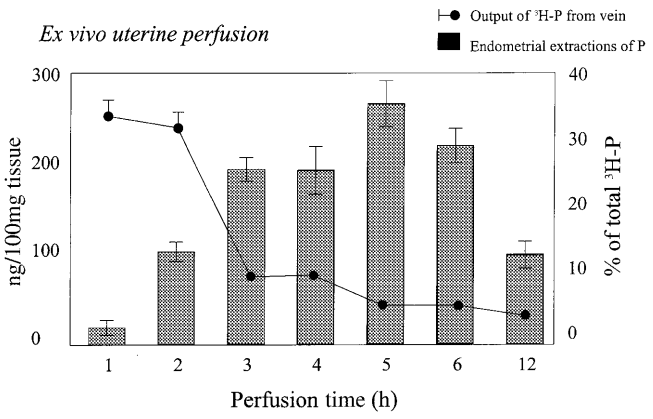

Figure 1. Direct (passive) diffusion through tissues from vagina to the uterus. Line graph: mean (± SD) per cent of total radioactive progesterone (^{2}H-P) that crosses the uterus (n = 30 organs) during 12 h following its vaginal application *in vitro* on the vaginal collar. Histogram: accumulation of radioactive progesterone in the endometrium. (Reproduced from Bulletti *et al*., 1997.)

transport of progesterone to the uterus could not result from conventional distribution by the circulatory system.

Passage through the cervical lumen from the vagina to the uterus

Passage through the cervical canal (aspiration) has been proposed as possible mechanism explaining the direct diffusion from the vagina to the uterus. Part of the vaginal gel applied against the uterine cervix and external cervical os could at least theoretically ascend through the cervical canal and reach the endometrial cavity with the facilitative effect of retrograde uterine contractility. Recent work, notably by Wildt's team, has provided evidence of intraluminal transport activated by uterine peristalsis (Kunz *et al*., 1996, 1998). Using sperm-size ^{99m}Tc-labelled macroaggregates of human serum albumin (Solco MAA, Solco Basel AG, Birsfelden, Switzerland), these investigators showed that during the late follicular phase elective transport takes place toward the tube on the side of the developing follicle. This phenomenon paralleled subendometrial uterine peristaltic waves with characteristic cervix to fundus dominance of displacement at this period of the menstrual cycle. Yet experimental data speak against this possibility. Characteristically, the time course of intraluminal transport is extremely rapid. In their study, Kunz *et al.* observed that Tc-99 activity migrated toward the 'dominant' tube within minutes of Tc-99 placement in the vaginal fornices. Such rapid transport contrasts with vaginal-to-uterus diffusion. Using an ex-vivo uterine perfusion model, Bulletti *et al.* showed that [^{3}H]progesterone placed on the rim of vaginal tissue reached the uterine fundus 5–6 h later (Bulletti *et al*., 1997). Furthermore, in the uterine perfusion model, the wave of [^{3}H]progesterone travelled at comparable speed in endometrial and myometrial tissues, reaching simultaneously the fundal area in these two tissues. Hence, the countercurrent diffusion to the uterus of substances placed in the vagina is a phenomenon distinct from intraluminal migration of spermatozoa or sperm-like particles.

Both groups of investigators have excluded interference between the two modes of transport. Wildt's team excluded the possibility of dissociation of Tc-99 from the albumin beads and subsequent vascular transport of 'free' Tc (Wildt *et al*., 1998). In their method, these investigators thoroughly washed the utero-tubal content after detecting tubal transport. The results showed complete disappearance of Tc activity, thereby confirming that migration of Tc activity truly represented intraluminal transport. Preliminary data obtained after sealing the cervical canal with latex also speak to contradict this possibility (de Ziegler *et al*., 1998). We can therefore conclude that the rapid intraluminal transport of spermatozoa and sperm-sized particles and the slower vaginal-to-uterus diffusion of vaginally administered substances such as progesterone are two distinct phenomena. Each mechanism however may be influenced by the state of uterine contractility (Fanchin *et al*., 1998).

The venous or lymphatic circulatory systems

Hormones placed in the vagina are absorbed as through other mucosae. Absorption is dependent upon transport in blood and/or lymph (Einer-Jensen *et al*., 1993). Besides absorption in venous blood, lymph may play an important role as it has been recognized to be an important carrier of steroid hormones (Magness and Ford, 1982, 1983). In swine, lymph originating from the mucous membrane and muscles in the cranial part of vagina are collected by small lymph vessels. The small vessels join to form two or three bigger vessels which run on each side of the organ, passing through the plica urogenitalis. Ultimately, these vessels unite with lymph vessels draining the caudal part of the uterus and end in the hypogastric, medial iliac and/or para-aortic lymph nodes. The lymph vessels from the most caudal part of vagina take a different direction to the superficial inguinal lymph glands (Einer-Jensen *et al*., 1993). A similar lymph drainage has been found in the cow (Jelinek and Kacer, 1973). In women, lymph vessels are also found that run from the cranial part of the vagina toward those originating from the uterine cervix, both ending into the hypogastric lymph glands (Williams *et al*., 1989). Therefore, the lymphatic system of the upper part of the vagina being in direct communication with those of the uterus may represent a potential route for direct passage to the uterus of substances applied into the vagina. Extension to the uterus of carcinoma of the upper third of the vagina supports the clinical relevance of this route of communication.

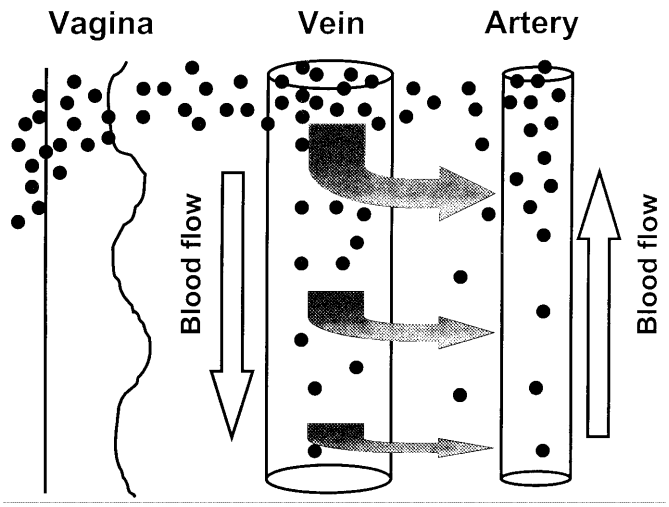

Figure 2. Countercurrent exchange system. Across the mucosa, the drug (•) reaches high concentration in local veins and lymph vessels. In the artery, the drug concentration increases progressively along the tract in which the vessels are in contact. At the end of this tract, drug concentration in the local artery will be higher than in arteries supplying other organs. While substances are normally transported from artery to vein, countercurrent exchange from vein to artery can take place if the following conditions are satisfied: (i) there is proximity with the exchange surface; (ii) there is a higher concentration in the venous flow; and (iii) the flow is in the opposite direction.

Countercurrent vascular transport with diffusion between utero-vaginal veins/lymph vessels and arteries

Principles of countercurrent transport

Countercurrent transport is a physiological exchange mechanism known to take place between fluids flowing in opposite directions. This can particularly take place between two fluid-filled tubes such as blood vessels that share a common (or very close) surface, and flow in opposite directions (Einer-Jensen, 1992). When this situation exists, exchanges can occur if substances are in higher concentrations in venous blood/lymphatic vessels than in the nearby artery. As normal substances transported in the circulatory system travel from artery to vein, transport in the opposite direction from vein to artery is logically referred to as countercurrent transport. Hence, through this system, the local arterial concentration of substances that diffused from the vein to the artery will become progressively higher than in arteries supplying other organs (Figure 2).

The physical basis for countercurrent transfer can be explained with a simple model. Consider two long copper pipes running in close proximity, with hot water pumped through one and cold water flowing in the reverse direction through the other. Heat will be exchanged between the two pipes so that the hot water flow is cooled by cold water running in the opposite direction. Clearly, in this example the cold water undergoes similar heat exchanges in reverse. By putting the hot and cold water pipes in close proximity, we have created a countercurrent heat transfer system. The magnitude of the temperature changes or efficiency of the countercurrent transfer system will depend on a variety of physical parameters. First among these factors are the size of the surface area common to both tubes, the nature of the metal (copper results in better heat exchange than plastic), and the flow rate (the lower the flow, the higher the exchange). This well-known technical principle is employed in steam engines and in ventilation systems (heat-exchange systems). The principle is based on a passive (no energy required) process which, in ideal conditions, may achieve near-100% transfer. In several organs of the body, blood vessels (veins and arteries) are actually arranged in a manner very similar to the tubes of our heat-exchange example (Figure 2).

The countercurrent transfer of heat, respiratory gases, minerals or metabolites has been described for many years as fundamental regulatory systems indispensable for several physiological processes. In sea mammals, wading birds and fish living in polar seas, countercurrent heat-exchange systems run in limbs, flippers or tail vessels in order to protect the organism against excessive heat losses (Schimdt-Nielsen, 1981). Because of countercurrent heat exchanges in their legs, ducks can stand with their wide, web-toed feet resting on ice without losing too much heat. In most mammals, countercurrent heat exchanges exist between arteries supplying the brain and veins carrying blood away from the nasal area and head skin. This is the basis for the so-called 'brain cooling system' which plays an indispensable role in protecting the brain against the risk of being exposed to excessive heat, for example in case of intensive exercise (Baker, 1979). The anatomical basis for the heat-transfer system resides in the pars petrosa of the temporal bone. There, in the cavernous sinus are drained the large veins flowing from the head and brain. It is not, however, the only venous outlet as these veins connect to large collaterals flowing more superficially. In this complex system, flow will follow vessels of lesser resistance. For example, venous outflow from the nose can pass either into the cavernous sinus or leave the area through the superficial veins on the face. Some animals have well-identified venous sphincters which control the venous drainage. The carotid artery runs inside the cavernous sinus, offering the anatomical base for a heat-exchange system. If cold blood flows in reverse in the sinus, it will efficiently cool arterial blood running in the carotid. Some animals have further developed this heat-exchange system with elaboration of the rete mirabile of the carotid segment embedded in the cavernous sinus. The rete mirabile is a mesh of short parallel thin arteries that carry the carotid flow. The multiplication of vessels increases the surface through which heat can be transferred between arterial and venous blood and thus facilitates the efficiency of the system.

Numerous other countercurrent (heat and chemical substance) exchange systems exist. In the boar for example, the pampiniform plexus participates in a countercurrent heat exchange that lowers the temperature of testes (Waites and Moule, 1961). The countercurrent transfer of minerals and metabolites in the kidney is a well-known system which helps in regulating the osmolarity and concentration of urine.

Countercurrent transport in the female pelvis

Anatomical structures suggestive of the local transfer of substances between the utero-ovarian vein and the ipsilateral ovarian artery have been described for some (e.g. cow, sheep, pig), but not all (e.g. horse), farm animals (Ginther, 1976). In women, the utero-ovarian veins also form a plexus running over the surface of the ovarian artery, thus forming the anatomical basis for countercurrent transfers. In animals, several experimental data have confirmed the existence of countercurrent exchanges occurring between pelvic vessels. When krypton-85 in saline was injected into a branch of the ovarian vein in the sheep, the gas was detected a few seconds later in the ipsilateral ovary with a mini-Geiger–Muller tube inserted into the corpus luteum; krypton-85 was not found in the contralateral ovary, thus excluding the possibility of recirculation via the general circulation (Einer-Jensen, 1988, 1992). Infusion of [^{14}C]progesterone into the ovarian vein in sheep induced higher concentrations of radioactivity in plasma collected from the ovarian artery during and after the infusion than in simultaneously collected plasma from the aorta (Einer-Jensen and McCracken, 1981; Einer-Jensen, 1992). A local transfer of follicular hormones from the ovarian to the utero-tubal arteries in pigs has been demonstrated and has been proposed as a mechanism regulating the oviduct function (Hunter *et al*., 1983).

The importance of actual transport of steroids through countercurrent exchanges in the pelvis has been questioned. The pool of free steroids in blood plasma is maintained in equilibrium with the pool of carrier-bound hormones, with only 1–2% of steroid hormones being unbound in the arterial blood. Although the efficiency of countercurrent transport from veins and lymphatic vessels to arteries has been estimated to be low, it must be considered that it can considerably multiply the concentration of free hormone in arterial blood that is able to interact with the receptor (Krzymowski *et al*., 1990). Demonstration of the occurrence of pelvis countercurrent exchanges also exists in humans. During laparotomy in women undergoing hysterectomy due to uterine fibroids, a mini Geiger–Muller tube was inserted into an ovary and krypton-85–saline infused into an ipsilateral vein. Radioactivity was registered during and after the infusion. The experiment was the first in-vivo indication of the existence of a countercurrent transfer system in women, as recirculation through the general circulation could be excluded (Bendz *et al*., 1979). Infusion of [^{13}C]progesterone into the uterine veins of a similar group of women induced a higher concentration of the hormone during and after the infusion in plasma samples obtained from the ipsilateral ovary than in parallel plasma samples obtained from both a peripheral vein and plasma samples from the contralateral ovary. When [^{13}C]progesterone was instilled into the uterine lumen, higher hormone concentrations were found in both series of ovarian samples than in simultaneously obtained samples from a peripheral vein, even if both tubes were ligated (Halket *et al*., 1985).

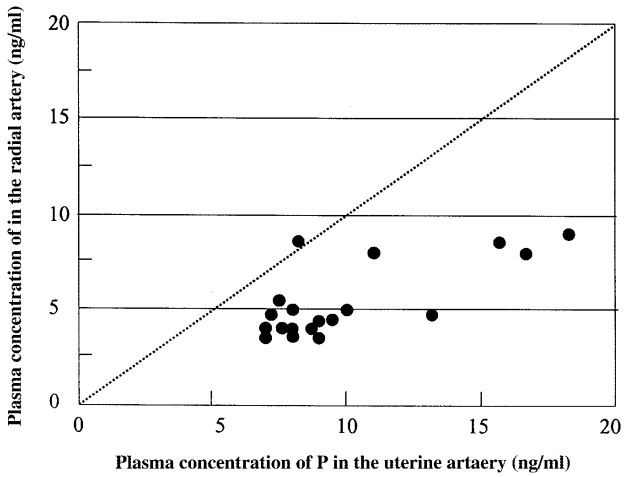

Figure 3. Countercurrent exchange of progesterone (P) administered vaginally. After vaginal administration, the plasma concentration of progesterone in the uterine artery is higher than that in the peripheral circulation (radial artery). (Reproduced from Cicinelli *et al*., 1998.)

Several types of substances, including prostaglandins, peptide- and steroid hormones, have been found to diffuse between venous and arterial vessels of the ovarian adnexae in laboratory animals, sheep, swine, cow and man (Einer-Jensen, 1988; Einer-Jensen *et al*., 1989; Krzymowski *et al*., 1990). The transfer of substances taking place in the tightly interconnected mesh of vessels of the ovarian adnexa has been shown to be the underlying mechanism of bi-directional interconnections between the uterus and the ovaries. Transfers have also been reported to take place from ovarian lymphatic to arterial vessels (Kotwica, 1980). As already stated, the lymphatic system is an important carrier of steroid hormones (Magness and Ford, 1982). Experimental evidence for transfers occurring from lymph to arterial blood has been reported by two independent groups (Heap *et al*., 1985; Krzymowski *et al*., 1987).

An anatomical relationship similar in appearance to that demonstrated in the adnexae, also exists between utero-vaginal venous plexus and uterine arteries (Williams *et al*., 1989). In the mesometrium, veins tightly entwine all the branches of the uterine artery. This creates a large area of close contact between veins and arteries that favours direct passage of substances between vessels. It has been observed in the pig that a large part of the surface of the branches of the uterine artery is covered with a thin-walled venous mesh; moreover, in the uterine artery

of the mesometrium it is also paralleled by numerous lymphatic vessels (Krzymowski *et al*., 1990).

Support for the hypothesis of local transfer between vessels resulting in countercurrent vagina-to-uterus transport was provided by Einer-Jensen and co-workers (Einer-Jensen *et al*., 1993). These authors found higher progesterone concentrations in the uterine arterial blood of pigs as compared with other arteries after vaginal administration of progesterone. We recently demonstrated that in women, hormone concentrations are also significantly higher in the uterine arterial blood than in the radial artery after vaginal administration of progesterone. At 45 min after single vaginal administration of a micronized progesterone (100 mg) in oil to 20 postmenopausal women undergoing transabdominal hysterectomy for benign pathologies, progesterone concentrations were nearly twice as high (9.75 ± 3.21 ng/ml) in the uterine artery as in the radial artery (5.12 ± 2.06 ng/ml) ($P < 0.000001$) (Cicinelli *et al*., 1998) (Figure 3). The results of this study conducted in a human in-vivo model, strongly suggest that the direct vagina-to-uterus transport of progesterone administered vaginally is mediated by a 'vagino-uterine countercurrent exchange'. These findings are consistent with those of others (Miles *et al*., 1994), and provide an explanation for the results reported previously. They also confirm that serum progesterone concentrations are not predictive of the effects exerted on the endometrium when progesterone is administered vaginally (Cicinelli *et al*., 1993; Fanchin *et al*., 1997). The possible existence of a countercurrent mechanism between vaginal venous plexus and vaginal and uterine artery is also in agreement with results of Bulletti and co-workers (Bulletti *et al*., 1997). In their human ex-vivo model, these authors observed a notable accumulation of [^{3}H]progesterone around vascular casts, thus indicating that preferential distribution to the uterus could be mediated through the vascular system.

Conclusions

In conclusion, we have summarized the accumulating body of evidence that supports a preferential distribution of progesterone to the uterus following vaginal administration. It is possible that all the above-mentioned mechanisms of distribution concur to target the effect of vaginal progesterone to the uterus. Hence, because of the elective delivery to its ultimate target organ, the uterus, vaginal progesterone will be preferred in several clinical situations—particularly when uterine effects need to be maximized (such as in infertility treatments) or blood concentrations minimized to limit side effects (such as in certain cases of HRT).

We have outlined animal and human experimental data that identify a local countercurrent vascular exchange system. This is likely to represent the underlying mechanism accounting for the local 'portal' transport between the vagina and uterus. There are good reasons to believe that countercurrent vagina-to-uterus substance transfer is part of a broader local vascular-supported intrapelvic exchange system that has more than one physiological role.

In certain species, countercurrent uterus-to-ovary transport of prostaglandins is likely to exert controlling influences of the uterus on corpus luteum function. In humans, the vagina-to-uterus local portal transport or 'first uterine pass effect' uncovered through studying vaginal delivery of hormones such as progesterone is likely to have definitive physiological significance that is unrecognized at present. Indeed, it is probable that prostaglandins contained in spermatozoa are the primary beneficiary of the newly discovered vagina-to-uterus transport. Delivered directly to the uterus, prostaglandins of spermatozoa can activate uterine contractility and help propel spermatozoa to the distal end of the tube without raising circulating concentrations of prostaglandins nor causing side effects. Therefore, the 'first uterine pass effect' is an underlying mechanism with probable physiological significance (transport of sperm prostaglandins) that has, until recently, remained ignored.

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