Preferential transfer of endogenous ovarian steroid hormones to the uterus during both the follicular and luteal phases

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BACKGROUND: Ovarian steroids are thought to be released into the systemic circulation and reach the uterus via the uterine arteries. However, results of experimental and clinical studies suggest the existence of local transfer of steroids from the ovary to the uterus. This study aimed to verify the existence of preferential distribution of ovarian steroids to the uterus in the two phases of the menstrual cycle. METHODS: We performed parallel measurements of serum levels of estradiol and progesterone in the systemic circulation (arterial and venous) and in the uterine vessels in two groups of cycling women; one group were in the follicular phase (six women) and the other group were in the luteal phase (10 women) of the menstrual cycle. RESULTS: Both in the follicular phase and in the luteal phase groups, mean estradiol levels in the uterine blood were significantly higher than in both sides of the systemic circulation ($F = 7.30$, $df = 15$, $P < 0.006$; and $F = 4.70$, $df = 27$, $P < 0.02$). Similar results were obtained in the luteal phase group for progesterone ($F = 9.38$, $df = 27$, $P < 0.0001$). Both estradiol and progesterone levels in arterial and venous systemic blood were similar. CONCLUSIONS: The results of this study demonstrate that ovarian steroid levels are significantly higher in the uterine vessels than in both sides of the systemic blood circulation, and strongly suggest the existence in the female pelvis of mechanisms of local distribution of ovarian hormones.

Key words: blood supply/local transfer/ovarian steroids/tube/uterus

Introduction

The uterus is the primary target organ for ovarian steroids as it undergoes profound transformations every month to permit blastocyst implantation. Traditionally, ovarian steroids are thought to be released into the systemic circulation and then reach the uterus via the uterine artery.

Based on the close anatomical and physiological relationships between ovaries and the uterus and the results of experimental and clinical studies, it is conceivable that mechanisms of local transfer of steroids from the ovary to the uterus exist. In the cow, the tissues adjacent to the ovary bearing the corpus luteum contain significantly greater quantities of progesterone than more distal tissues on the same side and all tissues on the contralateral side (Pope et al., 1982; Stefańczyk-Krzymowska et al., 1994). Due to the local transfer mechanisms (Bendz et al., 1979; Einer-Jensen, 1988; Einer-Jensen and Hunter, 2000), the ovarian steroids reach concentrations in the ovarian artery and tubal arterial arcade that exceed those measured in the systemic circulation.

The proposed explanation is that estradiol produced by the large follicle is locally transferred from the ovarian vein blood to the ovarian arterial blood, reaching a high concentration in the local arterial blood and inducing an increased blood flow to the organs supplied (ovary, tube, tubal part of the uterus). A similar transfer of progesterone may also be expected.

The existence of a local functional interplay between ovary, oviduct and uterus in women has been supported by bilateral ultrasonographic Doppler flow studies of the uterine arteries and of arterial Anastomoses between the uterine and ovarian arteries (junctional vessels) in the cornual region of both sides of the uterus during the menstrual phase of regularly cycling women. These studies demonstrated significantly lower resistance indices of the uterine artery and of the junctional vessels ipsilateral to the side of the dominant ovarian structure as compared with the corresponding arteries contralaterally (Santolaya-Forgas, 1992; Tan et al., 1996; Kunz et al., 1998). Accordingly, Ziegler
E. Cicinelli et al. (1999) demonstrated differences in the haemodynamic responses of the uterine artery compared with the radial artery during the menstrual cycle, suggesting a distinct regional control of the vascular response during the menstrual cycle.

The aim of this study was to verify the existence of preferential distribution of ovarian steroids to the uterus in the two phases of the menstrual cycle. For this purpose, we performed parallel measurements of serum levels of estradiol and progesterone in the systemic circulation (arterial and venous) and in the uterine vessels in two groups of cycling women, one in the follicular and the other in the luteal phase of the menstrual cycle.

Materials and methods

Sixteen premenopausal women 40–46 years of age were enrolled in the study that was approved by our Institutional Review Board. All patients received full information and gave their written informed consent. All the participants were regularly cycling as assessed by their reports of the last 6 months; in all of them, transcervical hysterectomy was indicated as complementary procedure for interventions of pelvic floor repair. All women were healthy and >6 months free from estrogen- and/or progesteron-containing medication. We excluded women with pathologies which could alter pelvic blood circulation (pelvic inflammatory disease, endometriosis, uterine myomas >2 cm, ovarian cysts and gynaecological cancers). Timing of surgery was decided based on the order of admission to the department; we operated on six women in the follicular phase between days 6 and 12, and 10 women in the secretory phase between days 18 and 25 of the menstrual cycle.

Before surgery, women underwent transvaginal pelvic echography using an Aloka 5500 sonograph equipped with a 5 MHz vaginal probe in order to assess the phase of the menstrual cycle and side of the ovarian functional structure (leading follicle or corpus luteum). The contemporary appearance of a double layer echo endometrium pattern not exceeding 8 mm thickness with a dominant follicle in one of the ovaries was used as the criterion for assigning the patient to the follicular phase; conversely, the appearance of a single band hyperechoic endometrium not exceeding 12 mm but greater than 8 mm of thickness together with a corpus luteum were considered as signs of the secretory phase.

After Pfannenstiel laparotomy and placement of an abdominal wall retractor, we took care to avoid any manoeuvre which could alter pelvic blood circulation. To this end, we did not place any forceps on the uterus or its ligaments and we decided not to isolate or separate the uterine artery from the veins but simply to aspirate a mixed blood sample from parauterine vessels.

Therefore, while gently keeping the intestine away from the pelvis and verifying the position of the leading ovarian structure, we pointed an 18 G butterfly needle towards the uterus. The needle was inserted into the anterior part of the broad ligament at the level of mid-uterine cavity, 1 cm lateral to the uterine side corresponding to the functional ovarian structure. A 2 ml aliquot of blood was aspirated through the plastic tube connected to the needle. Simultaneously, blood samples from the radial artery and the antecubital vein were also collected.

Blood samples were immediately centrifuged at 3000 g for 10 min; serum was collected and frozen at −20°C until assayed. The Immulite enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA) was used to measure serum progesterone [SI conversion factor 3.18; sensitivity 0.2 ng/ml (0.6 nmol/l; inter- and intra-assay coefficients of variation <10%)] and estradiol [SI conversion factor 3.67; sensitivity 12 pg/ml (44 pmol/ml; inter- and intra-assay coefficients of variation <10%)]

Data are reported as mean ± SD. Statistical analysis was performed by one-way analysis of variance followed by Student–Newman–Keuls test and by unpaired Student t-test. A P-value <0.05 was considered statistically significant.

Results

The average age of the women in the follicular and in the luteal phase was similar (43.6 ± 2.25 years, n = 6; and 44.3 ± 1.63 years, n = 10, respectively). In all cases, the ultrasonographic assessment of the side of the leading ovarian structure corresponded to the intraoperative assessment.

Blood sampling was easily performed in all cases.

In Table I, mean values of estradiol and progesterone in the mixed uterine arterial–venous blood, in the radial artery and antecubital vein in women in the follicular and luteal phase are reported; estradiol and progesterone serum levels in each woman are displayed in Figure 1. Significant differences between pelvic and systemic blood were found.

In the follicular phase group, mean estradiol levels in the uterine mixed blood were significantly higher than in the arterial and venous sides of the systemic circulation (F = 7.30, df = 15, P < 0.006). Serum levels in the radial arterial and antecubital vein were similar. The ratio between estradiol levels in the mixed uterine blood and the mean of arterial and venous systemic levels was 2.56. Progesterone levels were low in all samples and no significant differences were observed.

In the luteal group, both estradiol and progesterone levels in the uterine mixed blood were significantly higher than those found in either arterial or venous systemic blood (F = 4.70, df = 27, P < 0.02 for estradiol and F = 9.38, df = 27, P < 0.0001 for progesterone). On the other hand, both estradiol and progesterone levels in arterial and venous systemic blood were similar. The ratio between estradiol levels in the mixed uterine blood and the mean of arterial and venous systemic levels was 4.26, whereas that for progesterone was 2.35.

| Table I. Serum levels (mean ± SD) of estradiol and progesterone in the mixed arterial–venous blood (uterine vessels) and in both sides of the systemic circulation (radial artery and antecubital vein) in the follicular phase (n = 6 cases) and luteal phase (n = 10 cases) of normally menstruating women |
|-----------------|-----------------|-----------------|-----------------|
|                  | Uterine vessels | Radial artery   | Antecubital vein |
| **Follicular phase** (n = 6) |                  |                 |                 |
| Estradiol (pg/ml) | 201.80 ± 91.41  | 83.64 ± 48.61b  | 74.04 ± 42.06a  |
| Progesterone (ng/ml) | 1.21 ± 1.02    | 0.86 ± 0.49     | 0.75 ± 0.51     |
| **Luteal phase** (n = 10) |                  |                 |                 |
| Estradiol (pg/ml) | 223.66 ± 175.43 | 53.38 ± 23.75c  | 51.47 ± 24.27b  |
| Progesterone (ng/ml) | 23.67 ± 13.11  | 10.39 ± 3.69b   | 9.81 ± 3.38b    |

*p < 0.02; b p < 0.01; c p < 0.005.
The results of this study demonstrate that ovarian steroid levels are significantly higher in mixed arterial–venous uterine blood than in both sides of the systemic blood circulation. In other words, blood flowing around the uterus is much richer in ovarian hormones than would be expected from antecubital vein blood sampling. This strongly suggests the existence in the female pelvis of mechanisms of local distribution of ovarian hormones.

The existence of mechanisms of local distribution in the female pelvis has been demonstrated previously by the preferential distribution of xenobiotics and cold from the vagina to the uterus (Cicinelli et al., 1998; Cicinelli and De Ziegler, 1999; Einer-Jensen et al., 2001, 2002). Previous studies have also suggested preferential distribution of ovarian steroids to the tube and tubal part of the uterus ipsilateral to the functional ovarian structure (Einer-Jensen and Hunter, 2000). The data of the present study suggest that this preferential distribution of ovarian hormones also involves the corpus of the uterus. As it is known that venous blood from the upper part of the uterus drains into the ovarian veins (Kauppila, 1970; Kamina, 1993), the finding of a preferential ovary-to-uterus distribution delineates a new scenario of a local functional loop between the ovaries and all the upper genital tract.

Blood in the pelvic veins flows at a low pressure; even small variations in external pressure generated by intestine packing or spasm in veins caused by manipulation can significantly affect the quantity and direction of flow. Although separate arterial and venous measurements would provide a definitive understanding of physiological mechanisms controlling the pelvic distribution of ovarian hormones, in this pilot study we decided to measure hormone levels in the mixed uterine artero-venous blood in order to avoid any alteration induced by packing or manoeuvres of vessel isolation.

Therefore, we can only speculate on possible mechanisms at play. Partial drainage of ovarian hormones downwards to the uterine veins is the simplest mechanism that can be advocated to explain the higher levels in the mixed arterial–venous uterine blood compared with systemic blood. However, physiologically, venous blood flow goes mainly in the opposite direction from the uterus and tubes to the ovaries. Accordingly, during phlebography of the uterus, the ovarian drainage is faster than the uterine drainage; in the case of compression of ovarian drainage, the drainage becomes pelvic and in most cases good visualization of the uterine veins can be obtained (Kauppila, 1970). Similar blood flow distribution also occurs in animals in which a major part of the uterine vein blood leaves the uterus through a major uterine vein and joins with the ovarian vein to the large utero-ovarian vein which is close to the ovarian artery. Thus, substances secreted from the endometrium will reach the utero-ovarian vein blood and be transferred to the ovarian artery. This is how endometrial prostaglandin PG$_{2\alpha}$ induces luteolysis of the corpus luteum in domestic animals; it is metabolized to 95% by one passage of the lungs. If one interrupts the transfer system, the corpus luteum does not regress for several months (Ginther, 1981). We can also speculate that as we performed blood sampling in patients in a supine position, the upward drainage of utero-ovarian venous blood through the ovarian veins should be facilitated further.

Counter-current transfer in the ovarian pedicle from the ovarian veins or lymph vessels rich in ovarian steroids to the ovarian artery which anastomoses with the uterine artery in the tubal arterial arcade may constitute an alternative mechanism to explain the higher levels of ovarian hormones in the mixed uterine arterial–venous blood. In animals (pig, sheep), the occurrence in the meso-ovarium of a retrograde transfer of ovarian hormones involving blood and lymphatic vessels constitutes a local mechanism of ovarian secretion regulation (Einer-Jensen and McCracken, 1981; McCracken et al., 1984; Stefańczyk-Krzymowska et al., 2002). It has also been demonstrated in women that the ovarian steroids, by virtue of the local transfer mechanisms (Bendz et al., 1979; Einer-Jensen, 1988: Einer-Jensen and Hunter, 2000), reach concentrations in the ovarian artery and tubal arterial
circulation that exceed those measured in the systemic circulation.

A third mechanism for explaining our findings could be that the rich lymphatic network existing in the broad ligament may transport ovarian hormones to the uterus and to the uterine vessels by means of counter-current exchange. The main collecting system of the uterine lymphatics is formed from anastomoses of a lateral-uterine descending network of lymph vessels which unite with collecting vessels from the utero-ovarian pedicle and the external iliac area (Muckle, 1995). Local diffusion and high concentrations of hormones in tissues surrounding the ovary with the functional hypophysis may explain the difference in hematostasis, such a gradient was not evident.

A gradient of progesterone concentrations in tissues on the side ipsilateral to the corpus luteum; on the contralateral side, such a gradient was not evident.

The existence of a local distribution of ovarian hormones to the uterine vessels may explain the difference in haemodynamic variations observed in the uterine artery ipsilateral and contralateral to the functional ovarian structure (Tan et al., 1996).

It can be argued that the disappearance of the physiological intra-abdominal negative pressure is due to open surgery that could retard pelvic venous blood returning to the heart; however, as variation in external pressure around the ovarian and the utero-ovarian venous plexus is transmitted equally, the distribution of ovarian hormones between the two venous plexus should not be greatly influenced.

Our results disagree with those of Tourgeman and co-workers who measured the ratio of endometrial to serum estradiol in women undergoing ovarian stimulation or receiving exogenous estradiol. Since the ratio in stimulated women was lower than that calculated in women receiving vaginal estradiol, the authors concluded that estradiol produced by the ovaries is not preferentially delivered to the uterus (Tourgeman et al., 2001). However, the Tourgeman study was performed in artificial cycles in which the high levels of ovarian hormones produced may alter the physiological intra-pelvic blood circulation. The endometrial samples were obtained transcervically so that contamination of samples by the estradiol still present into the vagina could not be excluded. Moreover, they measured hormone levels in the endometrium whereas we assessed levels in the blood of uterine vessels.

The physiological importance of the local ovarian control of the uterus may be the ipsilateral impact of ovarian estradiol on sperm transport to the tube on the ovulatory side (Kunz et al., 1997). The process could ‘guide’ the sperm to the tube with the egg. Conversely, local high concentrations of progesterone will contribute to suppress uterine contractility in that area and allow the blastocyst to implant successfully.

In conclusion, the results of the present study demonstrate the existence of a preferential transfer of endogenous ovarian steroids from the ovary to the uterine vessels and support the hypothesis of a local functional loop between ovary, tubes and uterus.

References


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