A dominant ovarian follicle induces unilateral changes in the origin of the blood supply to the tubal corner of the uterus

E.Cicinelli1,3, N.Einer-Jensen2, R.Alfonso1, M.Marinaccio1, R.Nicoletti1, G.Colafiglio1 and M.Bellavia1

1Department of Obstetrics and Gynaecology, Bari University Hospital, Bari, Italy and 2Physiology and Pharmacology, Institute of Medical Biology, University of Southern Denmark, Odense, Denmark

3To whom correspondence should be addressed at: 1st Department of Obstetrics and Gynecology, University of Bari, Piazza Giulio Cesare, 70124 Bari, Italy. E-mail: cicinelli@gynecology1.uniba.it

BACKGROUND: The blood supply to the tubal corner of the uterus may originate from the uterine and ovarian arteries. The border of supply from the arteries has been found to move in young women; the change seemed dependent on ovarian steroid production. The present work investigated whether the border of supply could differ between the two sides of the uterus in the same woman having one dominant follicle (>10 mm). METHODS: Vagina was flushed with saline of room temperature in 15 women with a dominant follicle >10 mm. The temperature was measured in the mid-uterine lumen and in the tubal corner of the uterus at 2, 5 and 7 min after starting cooling. The investigation was repeated 30 min later measuring the temperature in the other tubal corner. RESULTS: The temperature decrease was, as found in previous investigations, more pronounced in the uterine cavity than in the tubal corners. However, a difference was found between the two tubal corners. At all measurement times the decrease was significantly smaller in the tubal corner corresponding to the dominant follicle than in the contralateral side. CONCLUSIONS: In our model, ‘cold’ is transferred from the vaginal venous blood to the uterine artery and the cooling defines the supply area of the uterine artery. Therefore, the results indicate that the area of supply from the ovarian artery in the tubal corner ipsilateral to the dominant follicle is greater than that in the contralateral side. It is possible to speculate that this difference is related to the hormonal production of the dominant follicle.

Key words: ovarian artery/tubal arcade/uterine artery/uterine blood supply/uterine corner supply

Introduction

In women the ovarian and uterine arteries in the same side are connected with a communicating artery supplying (at least part of) the Fallopian tube and the tubal corner of the uterus. The border between the two incoming flows in this communicating branch, and therefore the tissues supplied, is still a matter of debate.

In previous investigations in conscious women we have utilized a non-invasive method based on cooling of the uterine arterial blood to establish the ‘nutritional’ border between the uterine and ovarian arteries (Einer-Jensen et al., 2001, 2002). In detail, we cooled vagina with room temperature saline; the cooled vaginal venous blood cooled the uterine arterial blood (but not the ovarian arterial blood) through counter-current exchange. A probe equipped with two to eight points of measurement registered the uterine luminal temperature continuously. The uterine luminal temperature decreased in tissue supplied by the uterine artery, but only marginally in tissue supplied by the ovarian artery. The border between the two supplies was found in the tubal corner of uterus, 0.5–2 cm from the Fallopian tube entrance. In post-menopausal women the ovarian function influenced the exact position of the border that moved towards the uterine corpus in the follicular phase and in the opposite direction in the luteal phase suggesting the existence of a hormonal control of blood supply to tubes and uterus (Cicinelli et al., 2004a).

In previous experiments, temperature was measured only at the uterine corner ipsilateral to the ovarian functional structure (either dominant follicle or corpus luteum) and therefore we do not know whether the described variations in blood supply occur in both sides or only ipsilateral to the ovarian functional structure. The occurrence of similar haemodynamic changes at both sides should suggest that they are related to changes in systemic levels of ovarian hormones whereas unilateral changes should represent strong evidence in favour of the existence of local control mechanisms of blood supply to tubes and uterus.

The present investigation was performed in order to evaluate the influence of a dominant follicle on the position of the border by measuring the temperature decrease on both the ipsilateral and contralateral sides of the uterus in the same group of women.
Materials and methods
We enrolled 22 regularly cycling women, aged 28–41 years, complaining of light menstrual cycle disturbances (pre- and post-menstrual spotting or bleeding). All women had no evident pathology at transvaginal ultrasound and hysteroscopy had excluded the presence of any abnormality into the uterine corpus cavity (in all cases only cervical polyps were detected).

The local ethical committee approved the study protocol and the participating women gave informed consent.

All women had ovulatory menstrual cycles as documented by reports of regular menses and cyclical clinical signs of ovulation (mid-cycle increase in cervical mucus, pelvic pain, premenstrual symptoms etc.) during the previous 6 months.

Exclusion criteria were the presence of uterine myomas, ovarian cysts, genital malignancy, or uterine prolapse.

Women were requested to refer to our centre at day 11–13 of their menstrual cycle. Before the procedure, women had a transvaginal ultrasound in order to assess the phase of the menstrual cycle and determine the side of the dominant follicle. Only women with one dominant follicle (>10 mm) were included in the study.

The trial followed safe gynaecological procedures. Thermoprobes based on Cu/CuNi elements were used. A uterine probe made of stainless steel (ELLAB, Roedovre, Denmark) length 25 cm, and outer diameter (OD) 2.5 mm, blunt tip, was employed. The probe resembled a traditional uterine sound carrying a centimetre scale in order to give hysterometric evaluation; the probe was slightly curved 3–5 cm from the tip. Two thermoelements were built in: in the tip and 3 cm from the tip respectively. The probe was inserted inside the uterine cavity and directed towards the uterine corner until the tip was in contact with one of the tubal ostia so that consequently the lower thermoelement was in contact with one of the lateral limits of the cavity (Figure 1). Correct placement of the uterine probe was assessed by ultrasound and care was taken to maintain the same position of the probe throughout the experiment.

The probe was connected to an ELLAB thermometer (Model TM9604). The two temperatures were measured with a 2 s interval and transferred to a PC equipped with ELLAB’s Windows-based software. The traces were projected on the computer screen and the results saved in a file. Flushing of vagina with physiological saline (22–24°C) was started after 1–2 min when stable baseline results were obtained. The flushing was continued for 7 min; ~1 litre was used during this period. The probe was removed. The procedure was repeated after a 30 min rest period, the tip of the probe was now directed into the opposite tubal corner. The side of the first evaluation was randomized using a computer-generated randomization sequence (Epistat software, Round Rock, TX, USA).

Women were conscious during the investigation and no sedatives or painkillers were administered. All tracings were printed after the trial. All results from each patient were discarded if any of the tracings showed abrupt temperature changes, indicating movement of the tip. In total, seven patients were discarded, four in the group in which first measurement was ipsilateral to the leading ovarian follicle and three in the other.

Epistat software was employed to determine the sample size for a paired study in which the smallest difference between the two sides that we wanted to be able to detect was 20% with 95% certainty that the difference between the two sides was not simply due to chance.

The temperatures at the two points were measured before and 2, 5 and 7 min after start of cooling, using the ELLAB software. The temperature decrease, using the baseline temperature as the start temperature for each point at 2, 5 and 7 min was calculated. Data are reported as mean ± SEM. Paired Student’s t-test was used to calculate P-values. P < 0.05 was considered significant.

Results
The investigations were performed on day 12.1 ± 0.7 of the menstrual cycle; size of dominant follicle was 17.7 ± 1.2 mm.

Basal temperature at uterine corner (point 1) and mid cavity (point 2; Figure 1) was 37.32 ± 0.21 and 37.30 ± 0.22°C at ipsilateral side and 37.39 ± 0.36 and 37.37 ± 0.37°C at contralateral side. Basal temperature at point 1 ipsilateral to the dominant follicle was similar either when the recording was at the first or at the second (30 min later) vaginal cooling (37.32 ± 0.29 and 37.32 ± 0.14°C respectively).

The temperature changes 2, 5 and 7 min after starting of cooling at the uterine corner and mid cavity side ipsilateral and contralateral to the ovarian follicle are displayed in Figure 2A and B respectively.

At point 2 (uterine cavity), temperature started to decrease in all cases within a minute from starting the cooling. At 2, 5 and 7 min, temperature decrease at ipsilateral side did not differ from that measured at contralateral side; however, at time 2 min a trend to a greater cooling effect at the contralateral compared to ipsilateral was observed although the values did not differ significantly (−0.16 ± 0.04 versus −0.09 ± 0.03°C, at the contralateral versus ipsilateral sides respectively; P < 0.06).

At point 1 (tubal corner), the temperature decrease was smaller than at point 2 in all cases. However, when the temperature decrease at point 1 was calculated after 2, 5 and 7 min vaginal cooling, the decrease in the tubal corner ipsilateral to the follicle was significantly smaller than the decrease in the contralateral side. In contrast to all other situations, the follicular side temperature did not decrease with time so that after 7 min the temperature decrease was the same as that at 5 min (−0.04°C for both).

Discussion
The investigation demonstrated that during vaginal cooling temperature changes in the uterine corner ipsilateral to the
Follicle side has been previously demonstrated both in animals and humans. Mones and molecules from the ovary to the nearby structures of the ovary containing a dominant follicle are different compared to the contralateral side. In fact, at point 1 (tubal corner) ipsilateral to the ovary with a dominant follicle the temperature decreased less than at the other side and after a first decrease (2 min) it did not vary subsequently. Bearing in mind that in this experimental model 'cold' from vagina is transferred to the ovary (Tan et al., 1996; Kunz et al., 1998b), it is possible to hypothesize that the ovary and ipsilateral tube form a functional unit, which, in mono-ovulatory animals, creates a hormonal and functional unit somewhat different from that in the other side. The difference may favour sperm transport and the first days of life of the fertilized oocyte. This hypothesis is in accordance with several clinical data. Radiolabelled sperm were found after a few seconds in the ipsilateral tube side (Kunz et al., 1996). In spontaneous conceptions most chorionic sacs were found in the cornual region ipsilateral to the corpus luteum, indicating that there is no major migration of the blastocyst within the uterine cavity prior to implantation (Kawakami et al., 1993; Kunz et al., 1998b, 2000). Conversely, in cases of missed abortion a significant number of embryonic sacs was located on the side contralateral to the corpus luteum (Kunz et al., 2000). It is possible to hypothesize that, due to the different origin of blood supply and probably different hormone concentrations compared to the ipsilateral side, at the contralateral side less favourable conditions for embryonic growth are present.

The results from the present investigation support the results from our previous trials (Einer-Jensen et al., 2001, 2002; Cicinelli et al., 2004a). We constantly found that the temperature in the middle of the uterine cavity decreased more than in the tubal corners during vaginal cooling. However, the temperature, measured by the second thermoprobe at 3 cm distance from the tip, thus corresponding to the middle of the uterine cavity, showed a rapid decrease and only a trend to a non-significant, greater reduction in the contralateral side. This is in accordance with our previous investigations that demonstrated rapid transport of cooling from the vaginal venous outflow to the uterine artery.

As alternative to local changes in hormone levels or possibly as a cooperating factor in determining changes in blood supply and temperature transfer, changes in uterine contraction intensity and direction around the periovulatory period can be taken...
into account (Bulletti et al., 2000; Ayoubi et al., 2003). Around mid cycle, uterine contractility activity is characterized by high frequency retrograde contractions directed towards the tubal ostium ipsilateral to ovary containing the dominant follicle (Bulletti et al., 2000; Ayoubi et al., 2003). This in turn may help to explain the difference in variations in blood supply and cold transfer between the tubal corner ipsilateral and contralateral to dominant follicle.

This trial was made with a two-point metal thermoprobe resembling a uterine sound, since it made it easy to obtain a correct position in the uterus. We conclude that the border between the two arterial supplies moved, but we were unable to estimate the distance in millimetres. Construction of an eight-point metal probe may not solve the registration problem. The thermo-sensitive points will be separated by a few millimetres. They will, however, not be functionally separated since the metal sheet will act as a diffuser of the heat transmission. In any case, as point 2 mean temperatures at 2 min were close to being significantly different we can speculate that the influence of the ovarian artery reaches to 2–3 cm from the tubal ostium.

In conclusion, this study strongly suggests that substances from the ipsilateral ovary, possibly hormones secreted by the follicle, unilaterally will move the border of supply between the ovarian and uterine arteries. The border is situated in the tubal corner of the uterus and will move towards the uterine fundus. These findings are in agreement with the hypothesis of functional local interplay between ovary, tubes and uterus controlling sperm and oocyte transport, conception and early phases of life.

References
Cicinelli E, Einer-Jensen N, Barba B, Luisi D, Alfonso R and Tartagni M (2004a) Blood to the cornual area of the uterus is mainly supplied from the ovarian artery in the follicular phase and from the uterine artery in the luteal phase. Hum Reprod 19, 1003–1008.

Submitted on March 29, 2005; resubmitted on May 30, 2005; accepted June 3, 2005