Contralateral and Ipsilateral Arterial Vasculature of the Human Uterus: The Pilot Results of an Anatomical Study

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Summary

Arterial blood to the human uterus is provided by a pair of uterine arteries (UA) and supported by terminal branches of ovarian (OA) and vaginal arteries (VA). Literature reports the existence of ipsilateral and contralateral anastomoses between these arteries and the UA, but data on the prevalence of such anastomoses are discrepant. The aim of this trial is to study whether contralateral and ipsilateral anastomoses exist. We studied nine human uterine specimens, which were obtained from (i) human cadavers (n = 6), (ii) uterine transplant recipients (n = 2), and (iii) one altruistic uterine donor (n = 1). We injected India ink into the graft through the UA of each specimen (n = 8) or OA (n = 1). We semiquantitatively observed and evaluated the extent of the injection on horizontal, vertical, and transmural levels. The dye permeated beyond the midline in 9/9 (100 %) cases. Near-complete/complete permeation to the contralateral side was observed in 6/9 (66 %) cases. The dye permeated ipsilaterally throughout all uterine levels in 8/8 cases (100 %) of UA injection. The entire wall of the myometrium was permeated in 2/9 (22 %) cases. In 7/9 (78 %) cases, the wall of the myometrium was permeated less than halfway through. In conclusions, the preliminary results of this study prove the existence of ipsilateral and contralateral anastomoses. Complete transmural injection was observed in only 22 % of cases; however, this finding does not provide information about the functional capacity of these anastomoses. More data and studies are necessary to make definitive conclusions.

Key words

Anatomy • Blood supply • Collateral Circulation • Investigative Techniques • Transplantation

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Introduction

Much is known about the arterial blood supply to the human uterus. It is provided chiefly by a pair of uterine arteries (UA). The UA branches off mainly as the first branch from the anterior division of the internal iliac artery (IIA) or from the level of the inferior gluteal artery and superior gluteal artery (i.e., from a trifurcation) [1]. However, there are other less common areas from which UAs originate [1]. The UA typically follows a U-shaped course towards the uterus [2]. Initially, it extends caudally and laterally along the wall of the lesser pelvis (descending segment). From there, it turns medially and approaches the uterine cervix (horizontal part), crosses the ureter ventrally ('a bridge over water') and gives off one or two cervicovaginal branches. The cervicovaginal branches supply the uterine cervix at different levels [3] and form anastomoses with the vaginal arterial network. The third (ascending) segment of the UA runs along the lateral aspect of the uterus and gives off numerous arcuate arteries. Finally, the UA supplies the uterine fundus and splits into the terminal branches for the ovary, uterine tube, and the round ligament of the uterus [4-7].

However, the uterine blood supply is not derived solely from the UA. It is augmented by several other arterial branches, namely the terminal branch of the ovarian artery (OA), the vaginal arteries, and the artery of

the round ligament of the uterus [5]. The terminal branch of the OA connects to the branches of the ipsilateral UA and creates a vertical (ipsilateral) arterial arcade known as the utero-ovarian anastomosis (UOA). The existence of UOAs was discovered following non-target embolization into the ovaries during unsuccessful endovascular treatment of symptomatic uterine myomas [8-13]. Data on the prevalence of UOAs vary from 11 to 51 % of cases [6,8,14]. Arterial anastomoses in the uterine vasculature also exist between branches of contralateral UAs [5,6,15-17]. However, it is unknown if contralateral anastomoses exist as constant or variant structures. Hypothetically, if contralateral anastomoses were constantly present, they may simplify uterine transplantation (UTx) by reducing the number of required arterial anastomoses from 2 to 1.

This study aimed to verify the existence of contralateral and ipsilateral arterial anastomoses in the arterial vasculature of the human uterus.

Material and Methods

The sources of study material

This article is a morphological study of the arterial vasculature of the human uterus. The study protocol was approved by the Ethics Committee of the Institute of Clinical and Experimental Medicine and Thomayer University Hospital (identifier A-20-02) on February 12, 2020. The study is compliant with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [18].

A total of nine uterine specimens were obtained from three sources. The first source was a number of non-embalmed fresh human female cadavers that were subjected to autopsy. These cadavers provided a total of six uteri. A specialist in medical law provided consultation and formal approval with regards to the legal aspect of utilizing this source. The autopsies were performed at the Department of Clinical and Transplant Pathology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic. All of the cadavers were of Central European Caucasian origin. The uteri were procured en bloc with surrounding tissues.

The second source of uterine specimens comprised patients with a history of living donor UTx who needed to undergo graft removal. This source provided two uteri. The removals were performed five and a half years and four and half years after transplantation. Both procedures were carried out by Jiri Fronek. An anatomical study of the uterine arterial supply did not preclude a proper histopathological evaluation of the explanted graft.

The third source was an altruistic living donor who donated her uterus for transplantation. However, after procurement of the uterus, the uterine veins were considered too fragile to be anastomosed. As a result, the graft was contraindicated for transplantation but deemed suitable for anatomical study.

Anatomical study

First, the uterus was flushed through the bilateral IIA with lukewarm saline solution to clear vessels of blood and blood clots. We searched for leaking vessels and ligated them. Then we cannulated the unilateral UA. In one case (specimen 6), we used the OA in place of the UA for experimental purposes. The cannula was double-fixed to the vessel with a ligature. It was then connected to a syringe using a 1.8 mm polyethylene tube, which proved helpful since it prevented the cannula from becoming dislodged. The syringe was initially filled with lukewarm saline to rinse the vascular bed of residual blood. We then slowly injected approximately 20 ml of the diluted contrast dye (India ink, ratio of dilution 1:1) into the organ using gentle pressure. Only one artery was injected to verify whether the dye penetrated contralaterally and ipsilaterally throughout the entire uterus. We inspected the organ and photo-documented distribution of the dye throughout the organ. The uterus was then transected longitudinally along the median plane to evaluate dye distribution throughout the myometrium, and photo documentation was acquired once again.

In one particular case, the injected uterus was fixed in formaldehyde solution and dissected. Photos were taken for demonstration purposes.

Semi-quantitative analysis

The quantity (extent) of the contrast dye injection throughout the organ was evaluated along three perpendicular axes: (i) horizontal (contralateral), (ii) vertical (ipsilateral), and (iii) transmural. The extent of penetration for all axes was graded as mild (+), moderate (++), and near-complete/complete (+++).

Results

The results of the extent of injection are presented in Table 1. The injections of three uteri are visualized in Figures 1-3.

Table 1. Overview of uterine injection results

Specimen	Source	Extent of injection		
		Horizontal	Vertical	Intramural
1	living donor	+++	+++	+
2	cadaver	++	+++	+++
3	cadaver	++	+++	+
4	cadaver	+++	+++	++
5	cadaver	++	+++	+++
6	cadaver	+++ *	+ *	+ *
7	cadaver	+++	+++	++
8	explanted graft	+++	+++	+
9	explanted graft	+++	+++	++

* Injection was performed via the ovarian artery.

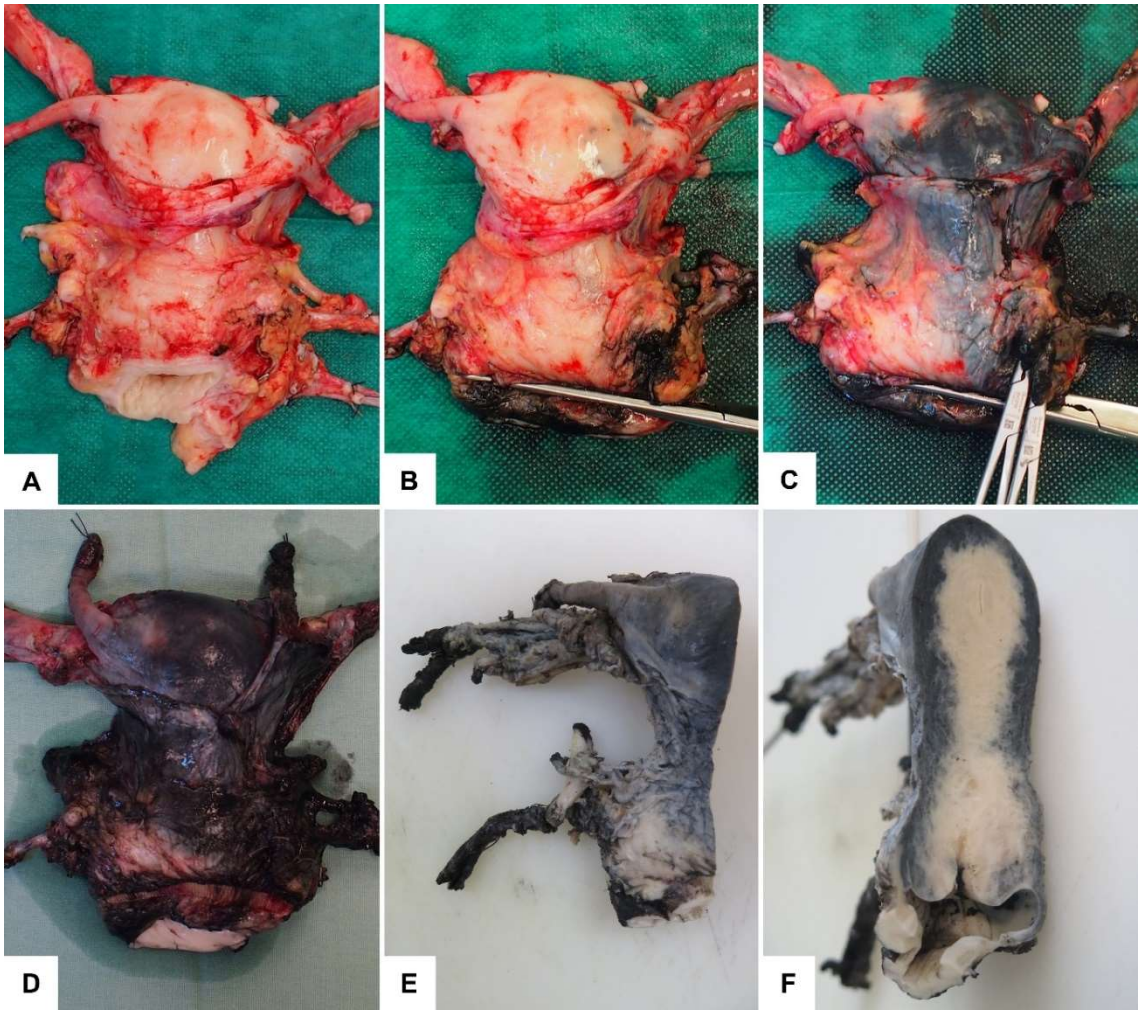

Fig. 1. The uterus, which was procured but contraindicated for transplantation due to fragile uterine veins. **A-D**) an anterior view of injection of the uterus through left uterine artery. **D**) permeation almost complete on vertical and horizontal levels. **E**) an anterior view of half of the uterus after fixation in formaldehyde solution. **F**) a lateral view of half of the uterus after fixation in formaldehyde solution. Poor permeation through the myometrium of the cervix, body, and fundus can be observed.

Transversal anastomoses

The dye permeated beyond the median line of the uterus in all cases (9/9, 100 %). Near-complete/complete permeation to the contralateral side of the uterus was observed in 6/9 (66 %) cases (Fig. 1-3). The dye penetrated approximately 2/3 of the uterine body in 3/9 (33 %) cases. The demarcation line was not straightforward but tortuous. In all cases where the extent of the injection at the horizontal level was found to be incomplete (with the exception of the one injected per OA), the area with the least amount of dye was that of the uterine body and fundus next to the contralateral uterine horn.

Vertical anastomoses

With regards to the UA injections (Fig. 1-3), the dye permeated ipsilaterally throughout all uterine levels in all cases (8/8, 100 %). In the case of the OA injection, the dye permeated ipsilaterally to approximately half the width of the uterine body.

Intramural anastomoses

The dye permeated the entire wall of the myometrium in 2/9 (22 %) cases. Intramural permeation was frequently non-homogenous. In most cases (7/9, 78 %), the dye permeated approximately halfway through the wall of the myometrium. The area that received the least amount of dye was the uterine body and fundus. Transmural permeation of the uterine cervix, on the other hand, was more evident. (Fig. 2,3). The reasons for such a result are unclear.

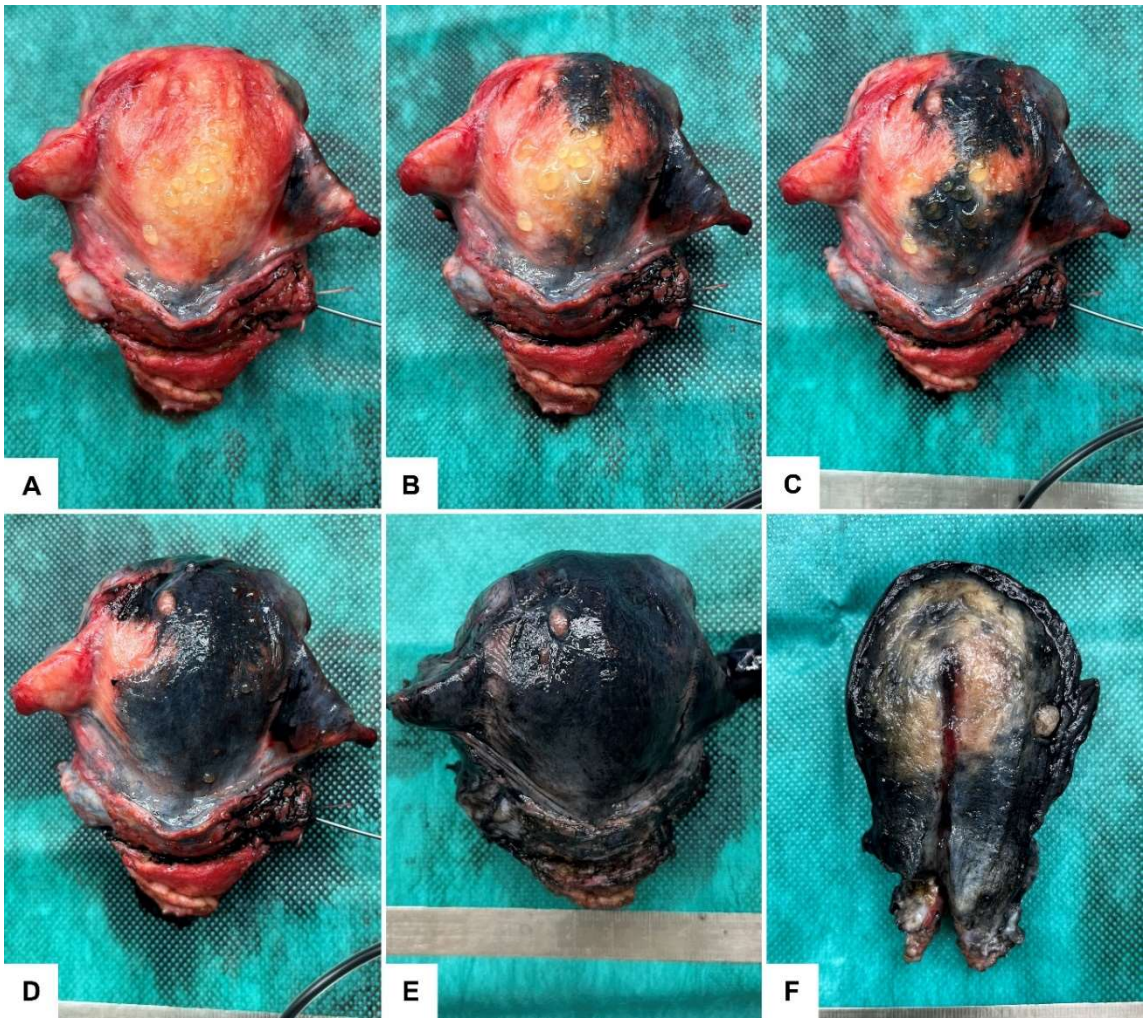

Fig. 2. The uterine graft explanted from a uterine transplant recipient. **A-E**) a posterior view of the uterus being injected through the right uterine artery. **F**) a lateral view of the uterus cut along the median line. While the myometrium of the cervix is permeated completely, only up to half of the myometria of the body and fundus are permeated.

Fig. 3. The uterine graft explanted from a uterine transplant recipient. **A-D**) a posterior aspect of the uterus is visible while the uterus is being injected through the left uterine artery. The myoma on the right posterior portion of the fundus (asterisk). A residual scar (arrowhead) from the C-section visible on the ventral aspect of the uterus (**E**). The surface of the uterus cut along the midline indicates near-complete/complete penetration of the dye throughout the myometrium of the cervix but minimal penetration through the myometria of the body and fundus. This could be partly due to the residual scar from the C-section (arrowhead) (**F**).

Discussion

There is a convincing body of evidence from both classic and recent literature supporting the belief that contralateral intrauterine anastomoses are constantly present in the form of multiple junctions of terminal branches of the arcuate arteries. Many famous anatomists reported the existence of contralateral uterine anastomoses, *e.g.,* Regnier de Graaf, Jan Swammerdam, Albrecht von Haller, and Josef Hyrtl [19-21]. Albrecht von Haller allegedly proclaimed, "*Omnes inter se communicant et una injecta turgent omnes*," which loosely translates as "All arteries communicate with each other, and when one is injected, all are injected."[21] This quotation is consistent with the results of our experiment. Josef Hyrtl, another notable anatomist, identified three types of uterine arterial anastomoses: transversal, vertical, and anteroposterior. He recognized the vast network of arterial anastomoses between different arterial branches of the human uterus. He masterfully depicted them in chromolithographic tables and published them in Die Corrosions-Anatomie und Ihre Ergebnisse [16]. There are three classifications of arterial branch localizations within the uterine wall: (i) subperitoneal (Fig. 4), (ii) submucous, and (iii) parenchymatous [21]. Many contemporary authors have reported the existence of contralateral anastomoses [1,5,6,22-25]. The preliminary findings of our study are consistent with the observations of such authors. For all specimens (n = 9), the dye applied to the single UA did penetrate the contralateral half of the uterus. However, in 1/3 of cases, the extent of penetration to the contralateral half of the uterus was incomplete. The reasons for such a phenomenon remain unclear. We hypothesize that arterial branches in the most distant contralateral parts of the uterus were not entirely void of residual blood clots and thrombi. Since the dye penetrated

beyond the midline (possibly in areas where the arterioles are at their smallest caliber) in all cases, we assume that incomplete permeation cannot be explained by the discrepancy between the caliber of ink microparticles and the vessel lumen.

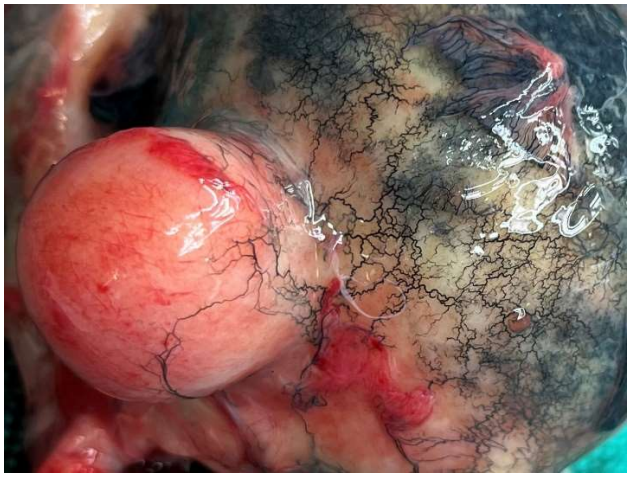

Fig. 4. A myoma of the explanted uterine graft in detail. On the right side of the photograph, a network of multiple arteriolar anastomoses is visible on the surface of the uterus.

Although contralateral arterial anastomoses are mostly microscopic, they may, at times, be macroscopically apparent. Pierre C. Huguier is credited with presenting a description of a transverse arterial anastomosis running around the uterine isthmus, which is known as Huguier's circle [21]. Herbert von Luschka observed a similar vascular pattern in the corporal portion of the uterus rather than in the cervical [26]. Von Luschka allegedly claimed that UA branches which create contralateral anastomoses on multiple levels of the uterine body could form "aneurysma cirsoides" [26]. Also, Lindenbaum *et al.* repeatedly observed abundant contralateral communications around the uterine cervix that constitute the "cervical collar" of vessels [15]. Some contemporary authors have observed macroscopic contralateral anastomoses between the right and left UA, albeit with different rates of prevalence. While Pelage *et al.* report the presence of transversal anastomoses in 9.8 % (19/194) of cases [6], Palacios Jaraquemada *et al.* report the presence of horizontal anastomoses in 38.5 % (15/39) of cases [5].

The UOA provides low-pressure communication between the lateral root coming from the OA and the medial origin stemming from the UA, located within the broad ligament of the uterus. Data on the prevalence of UOAs is rather heterogeneous, with varying results: 11 % (22/194) [6], 32.2 % (49/152) [8], and 51.5 % (104/202) [14]. There has been increasing interest in UOA in the past two decades due to its potentially profound clinical impact. Uterine fibroid embolization may lead to an ovarian failure caused by non-target embolization; it may also fail as a treatment due to incomplete embolization of the fibroid [14]. The direction and velocity of blood flow in a UOA vary between individuals. In most cases, the direction of blood flow in a UOA is from the ovary to the uterus. However, in 6-22 % of cases [8,14], blood flows in the opposite direction, i.e., towards the ovary (type III according to the Razavi's classification) [8]. So, in essence, local hemodynamics is more important than anatomy alone for determining the direction and velocity of blood flow through the UOA [23]. Furthermore, some authors report that a dynamic balance exists between areas supplied by the UA and the OA, depending on the menstrual cycle [23,27].

The clinical aspect of contralateral anastomoses should be clarified. Admittedly, it may be tempting to simplify the technical aspect of UTx, which is understandable considering the length of the procedure. The average length of a transplantation in the Czech UTx trial is 249±39 min [28]. An inflow based on a single artery, as opposed to two, might be sufficient for viability of the graft. This has already been successfully demonstrated in an experiment on a non-human primate. In a cynomolgus macaque, viability of the graft, gestation, and delivery were maintained by a blood supply from the unilateral uterine artery and vein, complemented by neovascularization from omental adhesions [29]. Furthermore, Rodriguez *et al.* reported three patients who had undergone radical trachelectomies (removal of the cervix, upper vagina and adjacent tissues). Two of the patients were subjected to bilateral ligation of UA; in all three a viable uterus with normal menstrual function was preserved [30,31]. This demonstrates that the uterus can remain viable via collateral circulation from the OAs [30,31]. However, if thrombosis of a single one UA develops shortly after human UTx, it is questionable whether an attempt should be made to salvage the graft. The probability of a salvaged graft being suitable for future conception and delivery is uncertain. Despite results obtained from the experiment and clinical experience mentioned above, it is not advisable to perform UTx with a single artery anastomosis. It is crucial to understand that UTx with two arterial anastomoses is in itself a simplified version of the procedure considering that the human uterus is physiologically supplied by six or more arteries: two UAs, two OAs (via the UOAs), and two or more VAs via

a dense collateral network [5,32]. Moreover, we believe that maximum perfusion of any transplanted organ should always be maintained.

This study presents several limitations, the most significant of which is the small sample size. Even though our preliminary results demonstrate the existence of ipsilateral and contralateral arterial anastomoses, the number of specimens is too low to draw definite conclusions. Furthermore, the presence of ipsilateral and contralateral anastomoses does not provide any information concerning the capacity of unilateral vessels to maintain uterine viability throughout pregnancy and delivery. Moreover, we feel that incomplete contralateral perfusion in some specimens might have been due to inadequate rinsing of the arterial network of blood clots and thrombi. Last but not least, the results of our study might have been limited by the presence of atherosclerosis.

Conclusion

The preliminary results of this study indicate that both contralateral and ipsilateral arterial anastomoses are constantly present in every human uterus. These findings are in accordance with numerous descriptions by various notable anatomists; however, our results do not provide any information regarding the functional capacity of one uterine artery to supply the entire uterus through contralateral anastomoses. It is not advisable to perform uterus transplantation with a single artery anastomosis. There is a need to acquire more data on this matter in order to draw a definitive conclusion.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Abbreviations

OA, ovarian artery; UA, uterine artery; UOA, utero-ovarian anastomosis; UTx, uterine transplantation;

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