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► To cite this version:

Fabien Robin, Ludivine Dion, Vincent Lavoue, Anna Goujon, Karim Boudjema, et al.. Relationship between uterine veins, ureter, and hypogastric nerve for uterine transplantation: An anatomic study. *Clinical Anatomy*, 2022, 35 (8), pp.1026-1032. 10.1002/ca.23850 . hal-03631187

HAL Id: hal-03631187

<https://hal.science/hal-03631187>

Submitted on 12 Apr 2022

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Relationship between uterine veins, ureter and hypogastric nerves for uterine transplantation: an anatomic study.

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Running headline: Uterine vein anatomy for transplantation

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Key words : Uterine transplantation, anatomy, uterine veins, ureter, hypogastric plexus

ABSTRACT (250 words including titles)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1002/ca.23850](https://doi.org/10.1002/ca.23850)

Background: Uterine transplantation is on the rise worldwide. In contrast to its arterial anatomy, venous drainage of the uterus is poorly defined in the literature. Our aim was to provide a standardized description of uterine veins through a multimodal approach to establish anatomical landmarks for the uterine transplantation surgeon.

Methods: Data were obtained from: (1) an anatomical study of eight fresh female cadavers (16 hemipelves) studied separately by an extrafascial dissection from the iliac bifurcation to the uterine pedicle, with analysis of the urinary tract and nerve structures; and (2) a virtual anatomical study from the Anatomage® Table comprising a high-fidelity virtual reconstruction of two deceased female subjects by imaging and anatomical methods.

Results: An inconstant duality of uterine veins was identified: a deep uterine vein of larger caliber, and a superficial uterine vein observed in 25% of cases. A close relationship of the ureter passing posterior to the superficial uterine vein and anterior to the deep uterine vein was evident in the parametrium. The inferior hypogastric plexus was identified in all cases immediately behind the deep uterine vein. The data obtained from the fresh female cadavers were validated by the Anatomage® Table.

Conclusions: We describe the close relationship of the uterine veins with the ureter and the inferior hypogastric plexus. This knowledge represents a surgical landmark to support the success of uterine transplantation by respecting both the graft and the safety of the living donor by limiting the risk of injuries during uterus procurement.

INTRODUCTION

Uterus transplantation (UT) is the only available treatment for women with absolute uterine factor infertility (AUI) caused by congenital or acquired absence of the uterus. In this setting, Brännström's team demonstrated the feasibility of the procedure for women who desired to become pregnant, and announced the first birth in October 2014 (Brännström et al., 2014, 2015). To date, more than 76 transplants have been performed worldwide, resulting in the births of 19 live children. UT is therefore a growing and promising technique for women with AUI to achieve motherhood (Dion et al., 2021). As most grafts are obtained from living donors (> 90% of UT performed), the main issue in the procedure is to prevent complications for the living donor while respecting the integrity of the graft. Two veins can be selected for removal: the utero-ovarian vein, which requires oophorectomy in the donor, and the uterine vein. According to Brännström, the most challenging step is the removal of the uterine veins, which is associated with an elevated risk of: ureteral injury (estimated at over 20%) (Chmel et al., 2021); venous lesions and subsequent thrombosis; and a greater operating time (Brännström et al., 2014). Furthermore, cases of postoperative bladder dysfunction in the donor could be related to this operating step (Chmel et al., 2019). However, in contrast to knowledge of the anatomy of the hepatic pedicle in the field of liver transplant (Hiatt et al., 1994), little is known about the anatomy of the uterine pedicle and the uterine veins. In classic textbooks, two uterine veins are described within the uterine pedicle (Gray, 2013), but the intimacy of their relationships to the ureter and the uterine artery within the parametrium is unclear. Also, there is a lack of knowledge of their caliber and of where they terminate in the internal iliac vein. These facts are as crucial for deceased-donor uterine procurement as for live-donor retrieval. Finally, available descriptions of uterine vein removal during uterine procurement are succinct.

We therefore aimed to provide a comprehensive standardized description of the venous drainage of the uterus in relation to the ureter and pelvic nervous tract through investigation of deceased subjects and digital reconstruction of female pelvises, with a view to establishing surgical anatomical landmarks for both living donor procurement and transplantation.

METHODS

Study design

The anatomical data were obtained from two types of source: i. sixteen hemipelves from eight female anatomical subjects dissected at the Rennes School of Surgery (anatomy laboratory of Rennes University); ii. digital reconstruction with the Anatomage® Table of four hemipelves from two additional female subjects.

The scientific committee of Rennes University ensured that written consent for body donation had been obtained and filed prior to death for all the anatomical subjects.

Our work complied with French regulations. The study was exempt from French law pertaining to biomedical research (the Huriet–Serusclat Law, 20 December 1998) as no additional interventions were required.

Anatomical study

Terminology

The second edition of the *Terminologia Anatomica* was used to avoid confusion in describing anatomical terms for the pelvic connective tissues (FIPAT, 2019). When a term was missing in the *Terminologia Anatomica*, we used unofficial but frequently cited terms (Ercoli et al., 2005).

Procedure

The dissection protocol consisted of making a median longitudinal abdominal incision from the xiphoid to the median of the pubic symphysis. For better exposure of the pelvis, the sigmoid colon and the upper rectum were sectioned and the entire digestive tract was reclined upwards. In four of the sixteen subjects, the dissection was done after arterial casting with red colored latex.

The following steps were repeated during the dissection of the 16 female hemipelves:

1) **Identification of the retro-ligamentous part of the ureter.**

We made a peritoneal incision to open the pararectal fossa at the lateral wall of the pelvis at the level of the iliac artery bifurcation.

2) **Identification of the internal iliac vein.**

We opened the medial pararectal space, also called the Okabayashi space, backward and laterally to the uterosacral ligament. **The hypogastric nerve was identified within this space.**

We then identified a vein that passed below the ureter, which we called **the deep uterine vein (DUV), within the paracervix.**

We also identified **the inferior hypogastric plexus (IHP) and the endings of the pelvic splanchnic nerves (PSN) within the paracervix.**

3) Identification of the ligamentous part of the ureter.

We dissected the ureter carefully downwards until it tunneled through the parametrium and crossed the ureterine artery, determining the **ligamentous part of the ureter. We respected the meso-ureter**, the anatomical structure that corresponds to a thin, sagittally-oriented connective mesentery enveloping the ureter within the presacral fascia (Ercoli et al., 2005).

We then identified the ligamentous part of the uterine artery.

4) Identification of a vein that passes above the ureter, which we called the superficial uterine vein (SUV), within the parametrium.

5) When possible, the vaginal artery was identified.

6) The uterine veins were followed until their termination in the internal iliac vein.

7) Identification of the venous plexus.

We sectioned the round ligament and then opened the anterior leaf of the broad ligament to access the mesometrium. Here, we identified the venous plexus and the ascending branch of the uterine artery.

Digital reconstruction with the Anatomage® Table

The Anatomage® Table (Anatomage, Inc., San Jose, CA) is a virtual dissection table created through imaging of real human anatomical subjects. Reconstructions combine data from the Visible Korean Project and the Visible Human Project. In both projects, cadavers were subjected to MRI and CT scanning and were then cut into sections ranging from 0.2 to 1 mm using a cryomicrotome; the slices were photographed with a digital camera. By combining computerized data, the table produces a real cadaver bed and demonstrates real patient data on a life-size scale (Ackerman, 1999; Park et al., 2006; Martín, 2018). These data are used for research with the agreement of the company Anatomage Inc. We provide a digital

reconstruction of the pelvic area from a deceased subject to illustrate our data highlighting the uterine veins, uterine artery, ureter, and the inferior hypogastric plexus.

Accepted Article

Results

Results from dissection of anatomical subjects.

Uterine veins

In all 16 hemipelves we identified the uterine venous plexus in the broad ligament within the mesometrium. In all cases, the venous plexus was accompanied by the ascending branch of the uterine artery (Figure 1). From this uterine venous plexus, one or two uterine veins emerged.

The superficial uterine vein

In four of the 16 hemipelves we identified the SUV coming from the uterine plexus and passing above the ureter. The SUV was very thin and always accompanied by the uterine artery at its caudal aspect. Thus, the SUV is within the parametrium (Figures 2 and 3).

The deep uterine vein

In all 16 hemipelves, a DUV was identified coming from the uterine plexus and passing below the ureter. The DUV has a caliber double or triple that of the SUV and is located within the paracervix. It is not a satellite to the uterine artery and runs posteriorly, cranially and laterally until it joins a short segment in common with the SUV. The two veins finally anastomose into a common uterine vein (Figure 3), which then terminates in the internal iliac vein at various levels.

Relationship with the pelvic ureter

The pelvic ureter closely related to the uterine veins.

Within the parametrium, the ligamentary ureter is crossed by the SUV (when present) and the uterine artery, and the DUV passes underneath. Thus, the ligamentary ureter is surrounded by uterine veins – the SUV in a cranial position, and the DUV in a caudal position – forming a triangle into which the ureter descends. The base of the triangle corresponds to the lateral border of the uterus, the upper side the SUV, and the lower side the DUV. The whole structure is directed laterally (Figures 2 and 4).

Relationship of the uterine veins to the pelvic autonomic nervous system

In all 16 hemipelves, the inferior hypogastric plexus (IHP) and pelvic splanchnic nerves (PSN) were identified in the paracervix. They were always situated below the ureter and the DUV. Thus, in the lateral aspect of the uterus, cranial-to-caudal, lie the uterine artery, the SUV (when present), the ureter, and the DUV. Consequently, the DUV is the most cranial [caudal?] element of the paracervix forming the roof of the IHP and PSN. Finally, the DUV is positioned between the ureter cranially and the IPH caudally.

Results from virtual dissection

The digital reconstruction of the pelvic area illustrates the results (Figure 5). The SUV was not seen in either of the two subjects. The DUV was located below the ureter and the IHP and PSN below the DUV. We made an animated movie of these results (Annex 1).

DISCUSSION

The present study provides a comprehensive description of the anatomy of the uterine veins, and highlights crucial relationships. We report that: (1) there are two uterine veins - the small and inconstant SUV, which runs cranially to the ureter, and the larger DUV, which runs caudally to the ureter; (2) these two veins describe an anatomical triangle with the medial uterine border where the ureter passes; and (3) the DUV is "sandwiched" between the ureter cranially and the hypogastric nerve plexus caudally. These findings have major surgical and clinical relevance to the field of UT.

In gynecology, while the uterine artery is precisely described, the anatomy of the uterine veins remains unclear. Moreover, definitions and description of the uterine veins are missing in the *Terminologia Anatomica* (FIPAT, 2019). The most detailed description of the pelvic veins seems to have been provided in 2004 by Kamina, who highlighted their avascular character and their topography in the parametrium and paracervix (Kamina, 2004). However, unlike the arteries, which have been extensively studied and are assessed before transplantation (Johannesson et al., 2012; Orhan et al., 2020; Leonhardt et al., 2021), the uterine vein dissection step is not well described. This is in contrast to liver transplantation, where the different types and frequencies of vascular anatomical variations are now well known, allowing the surgeon to anticipate difficulties and determine a reimplantation strategy (Hiatt et al., 1994). Additionally, to the best of our knowledge, there is a lack of original anatomical work on the anatomy of the uterine veins for UT. However, the step of uterine vein dissection is associated with pre- and post-operative complications for both the living donor and the graft (Jones et al., 2019). The dual digital and cadaveric approach developed in this work is innovative. Anatomage® data are derived from a combination of high-definition imaging data (CT, MRI) and cadaveric sections and thus constitute real high-fidelity anatomical models rather than a theoretical vision. This allowed us: (1) to evaluate the objective anatomical relationships of the veins in situ without the structural displacement secondary to surgical dissection artefacts; (2) to confirm the results observed in dissection, thus reinforcing the main message of the study; and (3) to illustrate the results for a better understanding of the uterine veins.

In the most recent series of uterine living donors, the rate of postoperative grade IIIB complications was over 11% (Dindo et al., 2004; Jones et al., 2019). This complication rate is similar to those reported for liver (10%) and kidney (8%) living donors. Among the major complications, ureteral injuries are predominant (20%) and far more frequent than in classic

intra- or extra-fascial hysterectomies (Nyangoh Timoh et al., 2019; Testa et al., 2020). Ureteral injuries negatively affect quality of life, potentially requiring a secondary ureter reimplantation in the living donor (Fageeh et al., 2002; Brännström et al., 2014). In the present study, we emphasize that the ureter is located in the center of a utero-venous triangle formed by the SUV cranially, the DUV caudally, and the lateral aspect of the uterus medially. Knowledge of this anatomical landmark is critical for protecting the ureter.

The success of other solid organ transplantations, such as the liver, has been achieved through precise knowledge of the relevant vascular anatomy and its variations. While the problem of inflow through the uterine artery is not an issue, that of venous outflow is a subject of debate, and routine practice varies across the world. Double ovarian and uterine drainage theoretically allows two options for venous anastomosis. Exclusive ovarian venous drainage would seem interesting because it avoids the need to dissect the uterine veins within the parametrium. However, it requires oophorectomy in 78% of cases (Dion et al., 2021) with the risk of induced menopause, and also has the highest failure rate of UT procedures (38%) (Jones et al., 2019). In addition, the ovarian vessels are of good caliber only in young donors. In the coming years, with an increase in older donors, these veins could be too small. Thrombosis is a threat in the event of poor drainage but can be avoided by good caliber regular veins and integrity of the vessels. We describe a duality of uterine veins – the DUV and the SUV – which until now has been poorly identified. Of the two, the DUV represented the larger and more constant drainage vessel in our dissections and we would therefore recommend this vein for graft drainage. The SUV, which was observed in 25% of our dissections, has probably been underestimated because of its fragility and small size in anatomical subjects. If both uterine veins are present, one solution could be to cut the SUV, procure the graft without injuring the ureter, and re-anastomose the transected SUV at the back table (Brännström et al., 2015).

In their review of the first 45 procedures, Jones et al. reported 28% of grade I-II complications, including consequences of nerve injury (Jones et al., 2019). These included postoperative functional sequelae such as fecal incontinence and urinary post-voiding dysfunction. The Czech team accurately described how to resolve bladder hypotonia by prolonged suprapubic catheterization (Chmel et al., 2019). Our work provides an explanation for these complications by describing the close caudal relationship of the DUV to the inferior hypogastric plexus. A nerve-sparing technique was standardized for endometriosis surgery by the team of Ceccaroni, who described the DUV as an anatomical landmark for nerve-sparing

(Ceccaroni et al., 2010). This technique decreases the risk of postoperative voiding dysfunction. However, even if the autonomic system can be identified, reproducible, nerve-sparing techniques have not been developed for all gynecological pelvic surgeries. We describe here the "sandwich" situation of the DUV with the ureter above and the IHP below as a major landmark for uterus harvesting.

On the basis of these results, with a view to protecting both the ureter and the autonomic system during uterine vein dissection, we propose the following: (1) to open the pararectal space to identify the IHP and PSN for nerve-sparing, (2) to identify the DUV, which is clearly visible within the paracervix owing to its greater caliber, (3) to dissect the retro-ligamentary ureter until it crosses the uterine artery, and (4) to identify the SUV. Here, the choice of sacrificing the SUV is possible. Once the DUV is free from the ureter cranially and the nerves caudally it can be removed safely.

The development of robotic pelvic surgery in recent years has led to increased accuracy in dissection. In both male and female surgery, nerve-sparing has become easier with improved vision (Magrina et al., 2011). This approach is being developed to minimize complications and trauma in the living donor and a trial evaluating the procedure is ongoing (NCT02987023) (Brännström et al., 2020; Johannesson et al., 2021). In addition, endometriosis surgery has emphasized the need to improve knowledge of the extraperitoneal region, particularly that of the nerves (Fermat et al., 2016; Kanno et al., 2021). Augmented reality techniques and the use of indocyanine green should increase the surgeon's ability to discriminate structures.

Despite our results, this study has some limitations. First, we included only a small number of anatomical subjects and, consequently, we probably did not capture the full range of variations. For example, termination of the DUV in the pudendal or gluteal veins can be observed in gynecological surgery, although it has not been described in the literature. Future studies on living donors are required to focus more on the modal and non-modal uterine vein anatomy to establish the full vascular pattern. Second, we worked mainly on elderly and menopausal cadaveric donors. Advanced age is accompanied by involution of the internal genital organs leading to a moderately different anatomy from that of the female candidate for uterine procurement. Finally, the small size and vacuity of the SUV could have led to their section during dissection, thus underestimating their frequency.

Conclusion

This study establishes a standardized anatomy of the uterine veins. It describes the very close relationship of the ureter passing between the uterus and SUV in the parametrium but also the posteroinferior relationship with the IHP. These data provide additional knowledge to the surgeon performing UT both to limit donor injury and to choose the best graft drainage.

ACKNOWLEDGEMENTS

The authors sincerely thank those who donated their bodies to science so that anatomical research could be performed. Results from such research can potentially increase mankind's overall knowledge that can then improve patient care. Therefore, these donors and their families deserve our highest gratitude (Iwanaga et al., 2021).

The authors would also like to acknowledge Jean-Eric Berton, Julien Landreau and Anatomage® for their technical support.

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FIGURE LEGENDS

Figure 1: Anatomical view of the left pelvis of a fresh female cadaver. Opening of the two peritoneal layers of the broad ligament.

We see the pelvic ureter (white arrows) within the parametrium and vein (black arrow) within the mesometrium.

Figure 2: Anatomical view of the right hemipelvis of a fresh female cadaver. Dissection of the parametrium and paracervix exhibits the duality of the uterine veins and the passage of the ureter. The superficial uterine vein is in front and the deep uterine vein behind.

UA: Uterine artery; SUV: Superficial uterine vein; DUV: Deep uterine vein; Ur: Ureter;

VA: Vaginal artery

Figure 3: Anatomical view of the right hemipelvis of a fresh female cadaver. Duality of uterine veins surrounding the ureter.

We see the deep uterine vein (white arrows) with the superficial uterine vein (white star) within the parametrium.

UA: Uterine artery; Ur: Ureter; ON: Obturator nerve; IIA: Internal iliac artery; EIA: External iliac artery

Figure 4: "Triangle of the ureter" corresponding to the lateral border of the uterus, the upper side the SUV, and the lower side the DUV. The shape is directed laterally.

Figure 5: Virtual dissection from the Anatomage® Table of a female left hemipelvis.

In green: the urinary system: the bladder, urethra and the ureter. In purple: the uterus and the vagina. In yellow, the inferior hypogastric plexus.

A. Deep uterine vein and its anterior relationship to the left ureter. The deep uterine vein is located below the ureter.

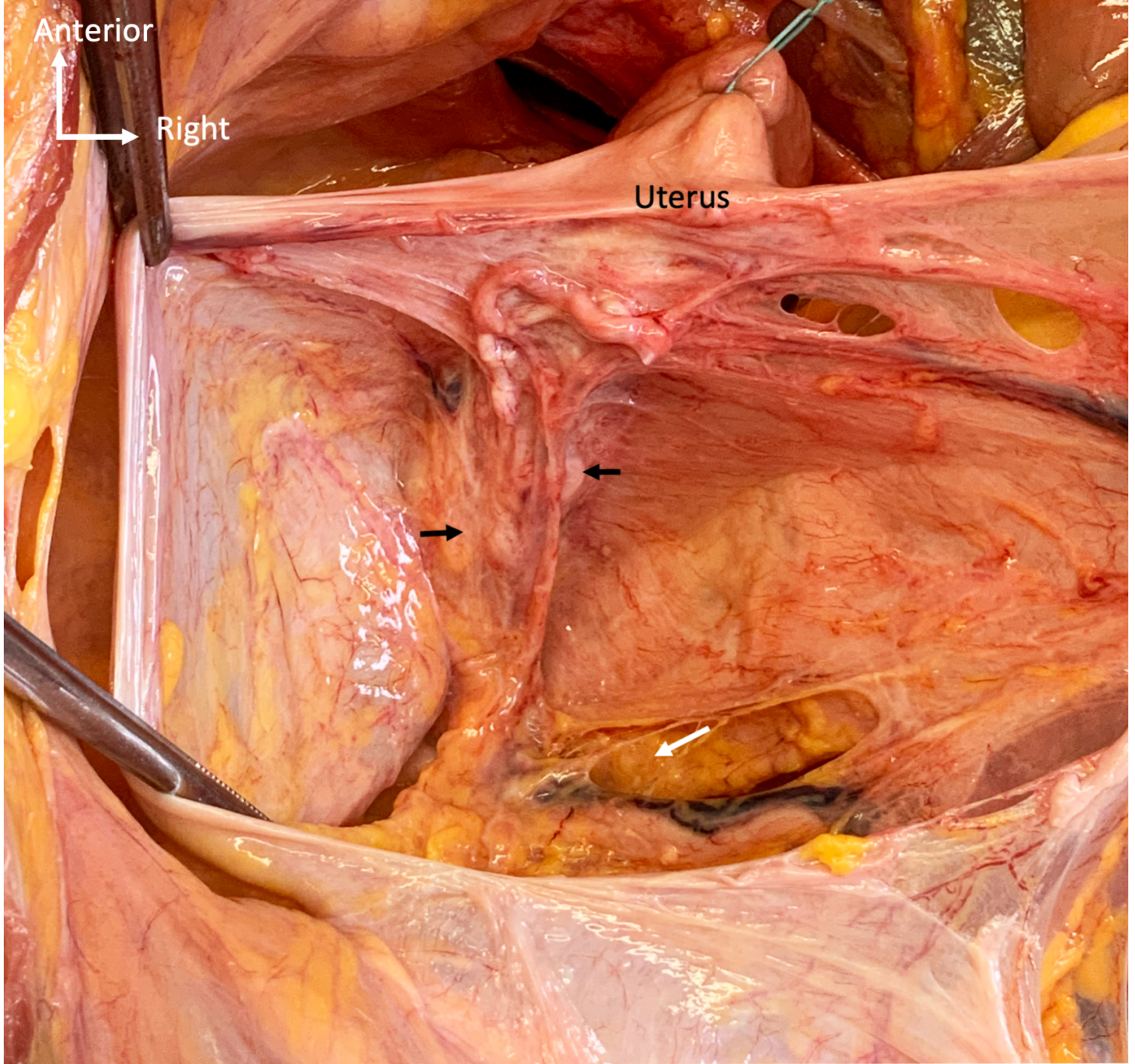
B. Addition of the branches of the internal iliac artery. The superficial uterine vein is not identified. We have highlighted the parametrium with the crossing of the ureter and the uterine artery (white arrow). We also demonstrate the close relationship with the vaginal artery

C. Addition of the pelvic autonomic nerve plexuses. The inferior hypogastric plexus (white arrow) is posterior to and closely related to the deep uterine vein

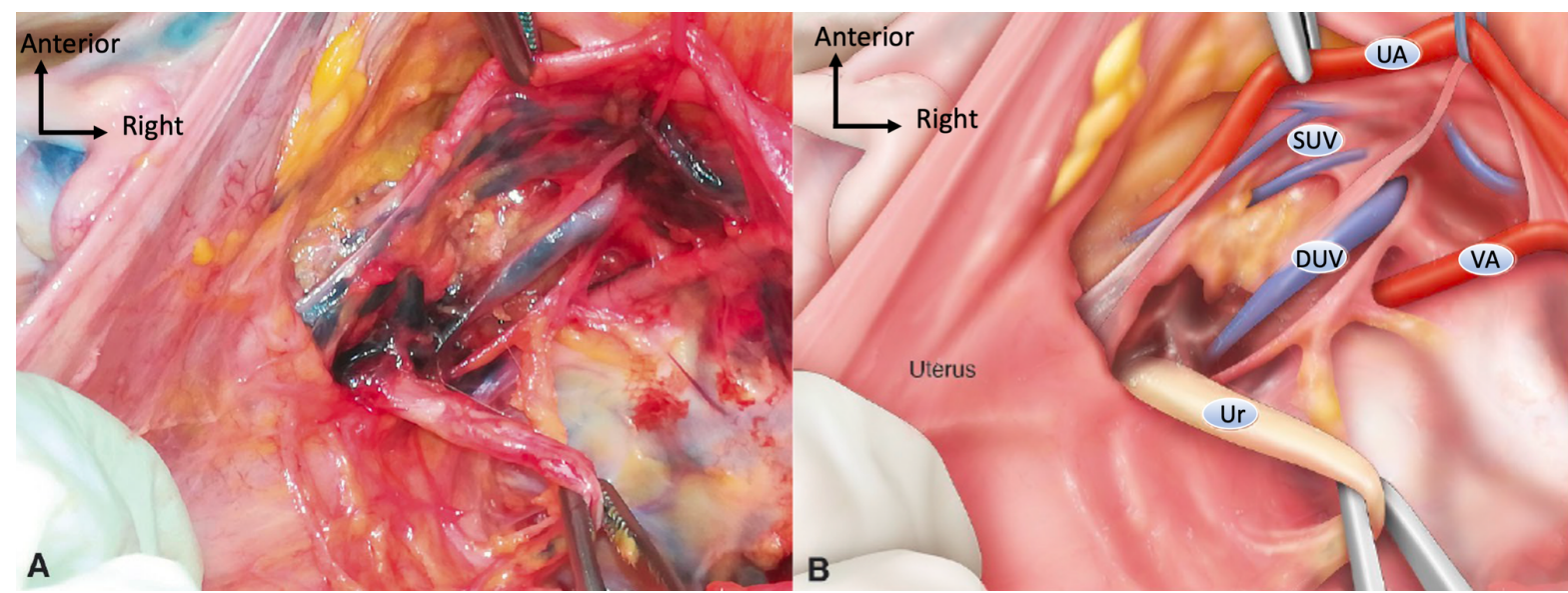
D. Relationship between veins and nerve tract without arterial branches

Supplementary file 1: An animation of the virtual dissection from the Anatomage® Table of a female left hemipelvis.

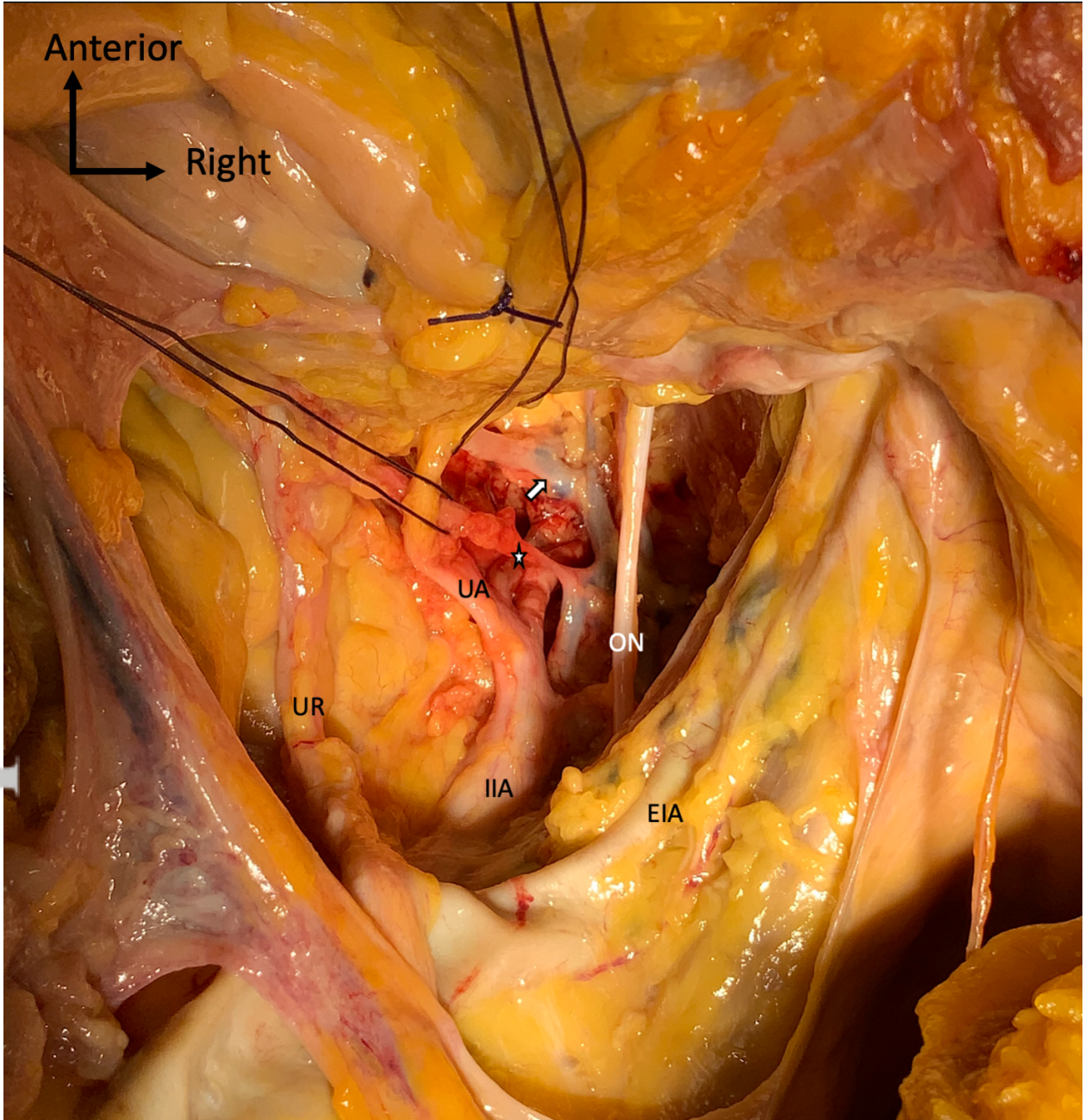
In green: the urinary system: the bladder, urethra and the ureter. In purple: the uterus and the vagina. In yellow, the inferior hypogastric plexus.



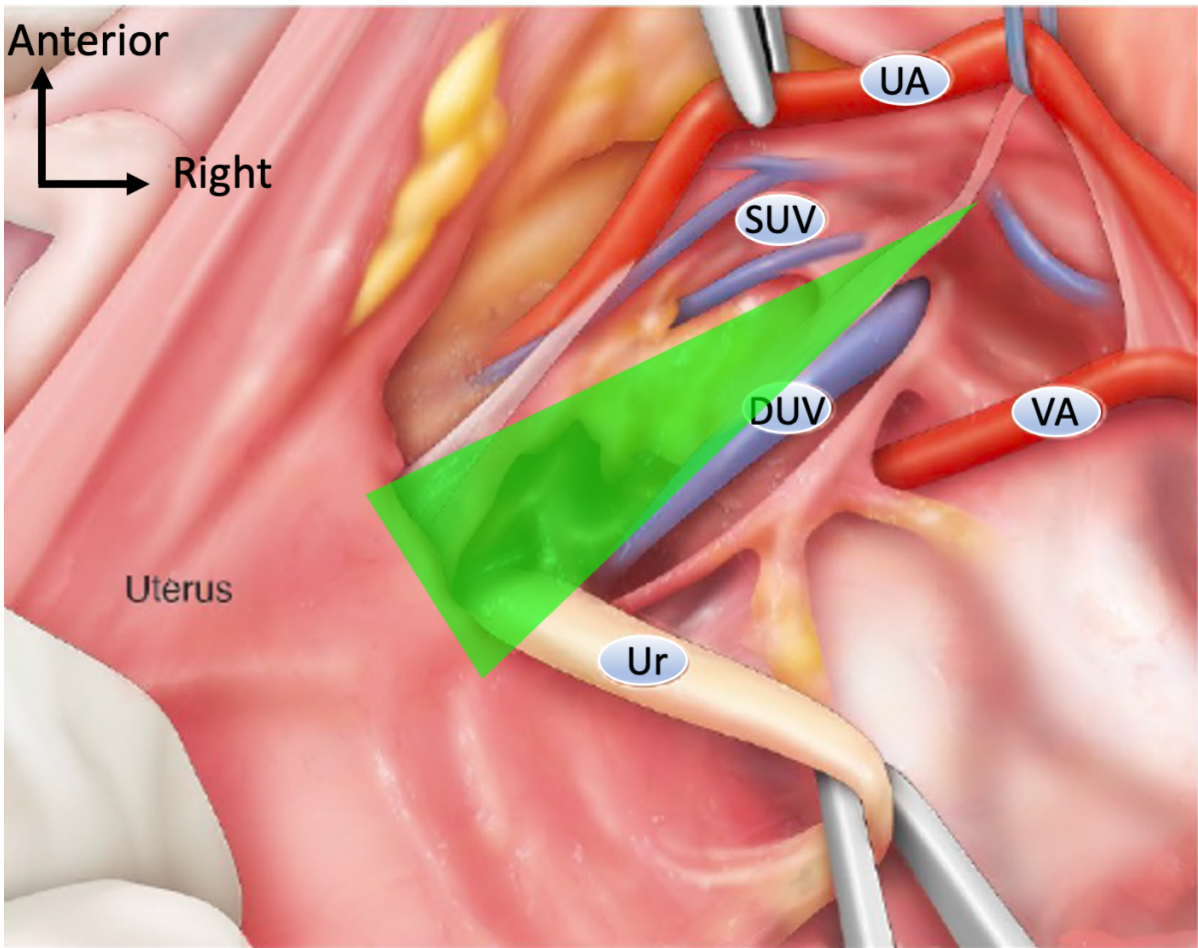
CA_23850_Figure 1.tiff



CA_23850_Figure 2.tiff

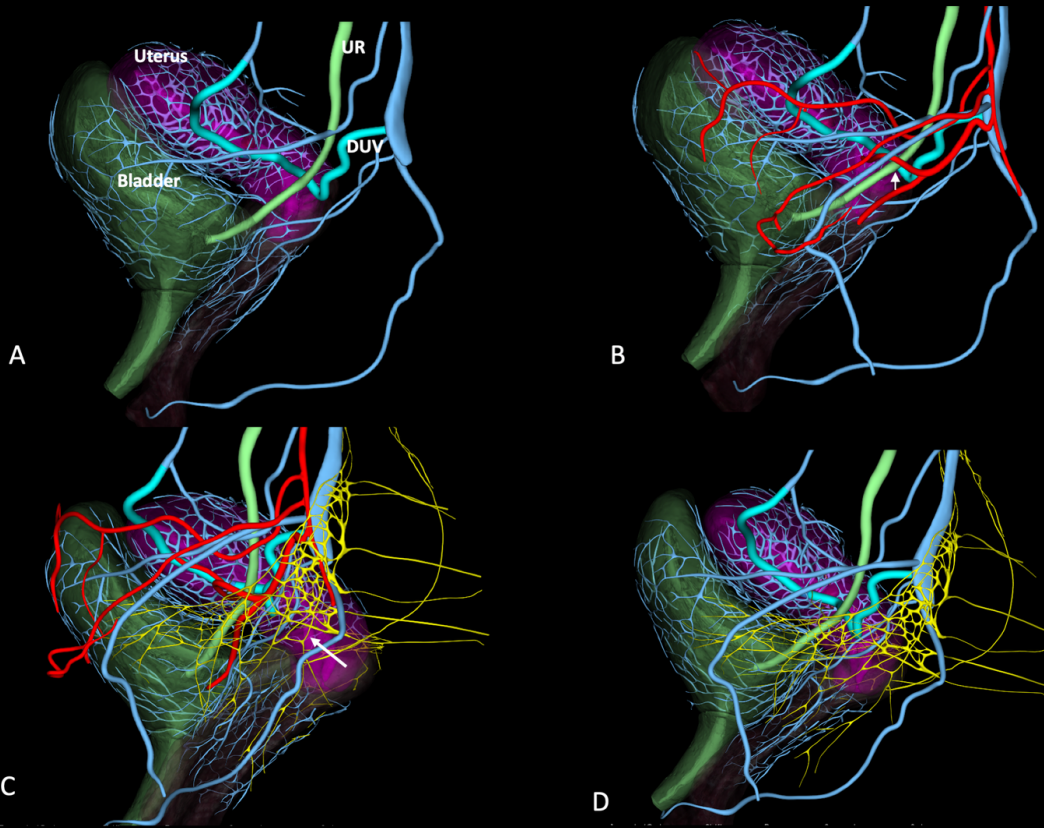


CA_23850_Figure 3.tiff



CA_23850_Figure 4.tiff

Cranial
↑
Posterior
→



CA_23850_Figure 5.tiff