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REVIEW

The Overview of Anatomical Variations and Congenital Anomalies of the Uterine Tubes and Their Impact on Fertility

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Summary

Anatomical variations and congenital anomalies of the uterine tubes (UTAVsCAs) are rare conditions, which are often undiagnosed, or accidentally diagnosed upon imaging, laparotomy, laparoscopy for unrelated condition, or during the Cesarean section. UTAVsCAs are often asymptomatic, but their clinical relevance lies in their possibly adverse impact on fertility. Since their rare occurrence, they are usually published as case reports. The most typically described are: agenesis of the uterine tubes (UTs), accessory UT (UT duplication), accessory UT ostium, and paratubal cysts (e.g. the hydatid cyst of Morgagni). UTAVsCAs are classified into an umbrella category of Müllerian duct anomalies (MDAs) which comprises anomalous development of all the organs developing from the paramesonephric (Müllerian) ducts, i.e., UTs, uterus and upper portion of the vagina. Interestingly, most of the classification systems of MDAs discuss solely the uterine and vaginal anomalies, while the UTs are often utterly ignored. This probably originates from the fact that UTs are no longer interesting for many clinicians as they think of UTs as superfluous organs whose function can be easily replaced in the *in vitro* fertilization (IVF) laboratory. Indeed, the modern reproductive medicine has been helping enormously with the conception of infertile couples. In many instances, the UTs are in fact successfully bypassed and a "test-tube" baby is born. Nevertheless, the UTs are still absolutely unique in providing suitable environment for fertilization and early embryo development - processes that has not been still completely understood. This fact could partially explain why the success rate of IVF is "only" around 30-50 % depending on age. Therefore, the research of the UTAVsCAs is still clinically relevant in the context of reproductive medicine and should not be omitted from research endeavors.

Key words

Anatomical variations • Congenital anomalies • Uterine tube • Fertility • Agenesis • Accessory uterine tube • Accessory ostium • Paratubal cysts • Terminological discrepancies

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Introduction

The uterine or Fallopian tubes *(salpinges)* (UTs) are approximately 10 cm long muscular tubes extending from the vicinity of each ovary to the horns of the uterus. The UT occupies the upper portion of the broad ligament referred to as the mesosalpinx. The UT can be subdivided into several anatomical regions. Nearest the ovary is the funnel-shaped portion, the *infundibulum* opening into the pelvic portion of the peritoneal cavity. The edges of the infundibulum have finger-like projections, the *fimbriae*. During ovulation, the ovum is captured by the infundibulum and is transported by the ciliary beating of the tubal epithelial lining in the direction of the uterus. The next anatomical part is the wide *ampulla* (the usual site of fertilization), then the narrower *isthmus*, and finally there

is the part of the UT that runs within the uterine wall, the intramural (uterine) portion [1,2]. The uterine / intramural portion of the UT has a small lumen, a millimeter or less in diameter, although the lumen tends to increase in size towards the ovarian end (around 2 mm or less in diameter) [3]. The UTs have principal role in the processes of sperm and ovum / early embryo transport, as well as support of the ovum / early embryo by nutritional resources provided by secretions of the lining epithelium. Recent studies have shown that the UT microenvironment is critical for the embryo development and its future health as an adult due to epigenetic programming [4].

From the historical perspective, the main breakthrough in the study of the UTs can be dated to the Enlightenment period, also known as the "Age of Reason", which put the main emphasis on rigorous scientific study. In this very period, one of the greatest anatomists of all time by the name of Frederik Ruysch (1638-1731) was born in Netherlands. Over the course of his active career, he was able to dissect and document countless normal and abnormal specimens, many of which are still an integral part of the exhibition in the Peter the Great Museum of Anthropology and Ethnography (Kunstkamera) in Saint Petersburg (Russia). One of such exhibits is the so called "Case 47" depicting the anatomical preparation of the female internal genitalia with three UTs [5]. Netherlands in its Golden Age of science and technology was a bottomless well of game-changing scientists. Another UT anomaly, namely its abnormal length was first described by none other than Regnier de Graaf in his famous work *De Mulierum Organis Generationi Inservientibus 1672*, published only one year before his untimely death [6]. Depending on the type and severity of the anomaly, it can either go absolutely unnoticed or the first symptoms will not become evident until puberty, first sexual intercourse or fertility problems. Shöller *et al.* [7] summarized that the current incidence estimates of female reproductive system congenital anomalies (FRSCAs) are around 0.2-0.4 % in the general population, rising to 3-13 % in patients diagnosed with and/or treated for infertility. However, estimating the true incidence of such rare conditions is almost impossible because they are often diagnosed by chance. Despite the fact that anatomical variations and congenital anomalies of the uterine tubes (UTAVsCAs) belong to the umbrella category of paramesonephric Müllerian duct anomalies (MDAs), they are sporadically mentioned and classified. In most cases, the emphasis is put mostly on uterine anomalies [8]. Strikingly, Robbins *et al.* [9] published a review paper on MDAs in which the authors stated that MDAs are congenital anomalies affecting the uterus, cervix and vagina. The UTs were not even mentioned in their definition.

The main purpose of this review article is to provide an overview of selected anatomical variations and congenital anomalies of these important, yet neglected organs, from the perspective of their embryonic origin, diagnosis, management, classification, and clinical significance related to assisted reproduction techniques.

Short Embryological Overview of the Development of the Female Internal Reproductive Organs

From the embryologic perspective, the UTs represent the cranial ends of the paired paramesonephric Müllerian ducts, the caudal ends of which fuse together to form the unpaired uterus and the cranial portion of vagina. At the end of the sixth week, the bipotential phase of the genital system development comes to an end. The paramesonephric Müllerian ducts develop laterally to the mesonephric Wolffian ducts as a craniocaudal invagination of the thickened coelomic epithelium of the posterior body wall. The cranial ends of the paramesonephric ducts open into the coelomic cavity and caudal tips cross the mesonephric ducts medially to fuse just before they open into the urethral portion of the urogenital sinus. In this phase, male and female genital systems are indistinguishable, but from the seventh week on, the development of the genital system pursues either of the two divergent pathways. In the female embryo, the XX somatic cells lack the Y chromosome and its SRY gene. That is why the cells inside the female gonads differentiate into ovarian follicular cells instead of testicular nurse cells (of Sertoli) responsible for the production of the anti-müllerian hormone. The absence of anti-müllerian hormone causes persistence of the paramesonephric ducts which are stimulated to differentiate into the UTs, uterus and the cranial portion of the vagina, whereas the mesonephric ducts degenerate. The dorsal wall of the urethral portion of the urogenital sinus forms a local thickening called the sinusal tubercle, just at point where the fused paramesonephric ducts open into the urogenital sinus. Once fused, the caudal tips of the paramesonephric ducts merge with the sinusal tubercle of the urogenital sinus and then start to fuse together in the cranial direction to form unpaired midline short hollow tube called the uterovaginal primordium. It gives rise to the uterus and presumably also the cranial portion of the vagina. Unfused

cranial portions of the paramesonephric ducts give rise to the UTs [10,11].

In scientific literature, congenital anomalies and anatomical variations of the uterus and vagina are more commonly described than those of the UTs. The embryological background of these anomalies is usually the failure of fusion of the Müllerian ducts, whole or partial duplication of the Müllerian duct on one side (splitting of the duct during the 7th week of development) or partial or total agenesis of the Müllerian duct on one side or both sides [12]. With the decline of the mesonephros during embryonic development, the mesonephric Wolffian ducts and its tubules in the female embryo lose their primary function and regress. In the close vicinity of the female internal reproductive organs, microscopic vestigial remnants of the mesonephric Wolffian ducts can be observed. In adult females, the obliterated Wolffian duct begins near the ostium of the UT and runs in the broad ligament. It enters the uterine wall above the cervix and continues downward in the cervical and vaginal walls to end near the vaginal orifice. All these remnants of the Wolffian ducts are rarely detected unless pathologic changes develop. Since these anomalies result from the incomplete regression of the Wolffian ducts, and thus don´t belong to the MDAs, we will only mention them and won´t be covered in detail. These anomalies are: appendix vesiculosa (sessile hydatid) as a remnant of the blind head of the Wollfian duct, epoophoron (Rosenmüller´s organ), paraoophoron (tubes of Kobelt) and Gartner´s canal (*ductus epoophori longitudinalis*) from the distal portion of the Wolffian duct in the cervical or vaginal wall. However, we will mention the hydatid cysts of Morgagni, since their embryonic origin is unclear and these cystic structures are in direct anatomical contact with the fimbriated end of the UTs. The hydatid of Morgagni is a benign, small (usually around 1–2 cm), pedunculated serous fluid-filled cyst arising from the fimbriated end of the UTs. According the first hypothesis, the hydatids of Morgagni are developmental remnants of the Wolffian duct [13,14]. According to the second hypothesis they are Müllerian duct remnants [15-17].

Controversies in the Classification of Congenital Anomalies of the UTs

Currently, there are several classification systems focused on FRSCAs. The first systematic classification dealing with MDAs was published in 1907 [18]. In 1979, Buttram and Gibbsons [19] developed a classification system based on the development of the FRS. It was modified in 1988 by the American Society of Reproductive Medicine which proposed seven different types of MDAs (Fig. 1) [20]. The classification system describing embryological origin of the organs of the FRS was proposed in 2004 (Table 1) [21,22].

Acien *et al.* [23] analyzed all existing classification systems in their study. They classified FRSCAs as MDAs caused primarily by the agenesis and/or insufficient fusion of the Müllerian ducts. They also analyzed other classification systems based on different aspects: functional, defects in vertical fusion, embryological, or anatomical (Vagina, Cervix, Uterus, Adnex and Associated Malformation: VCUAM classification). However, it is important to note that all published/mentioned classification systems focused on FRSCAs/MDAs do not primarily deal with the UTAVsCAs. They are not even mentioned in the *Terminologia Embryologica* [24].

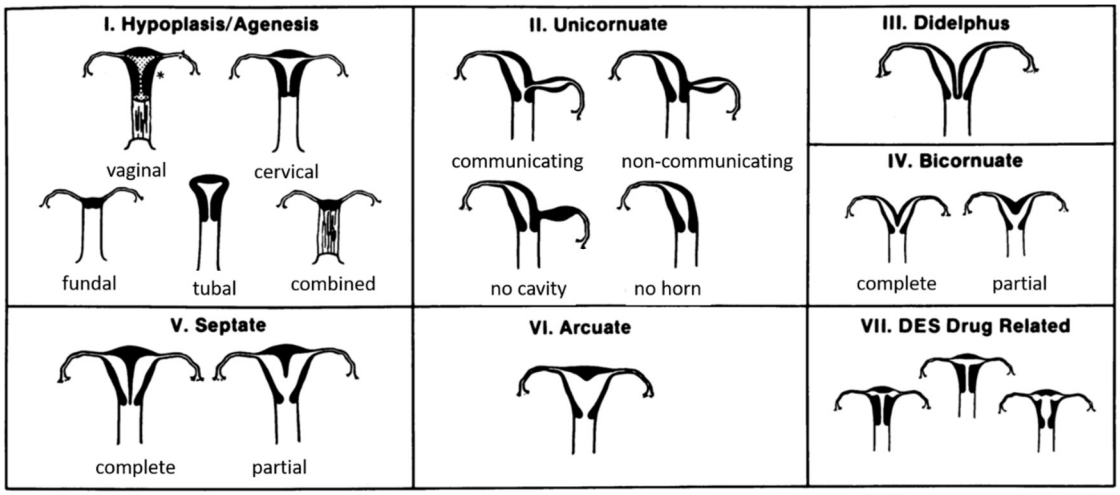

Fig. 1. The American Fertility Society classifications of Müllerian anomalies [20].

Table 1. Clinical and embryological classification of the malformations of the FRS according to [21,22].

1. Agenesis or hypoplasia of a whole urogenital ridge	Unicornuate uterus with uterine, tubal, ovarian and renal agenesis on the contralateral side
2. Mesonephric anomalies with absence of the Wolffian duct opening to the urogenital sinus and of the ureteral bud sprouting (and therefore, renal agenesis)	Utero-vaginal duplicity plus blind hemivagina ipsilateral with the renal agenesis, clinically presented as: a) Large unilateral hematocolpos b) Gartner's pseudocyst on the anterolateral wall of the vagina c) Partial reabsorption of intervaginal septum, seen as a 'buttonhole' on the anterolateral wall of the normal vagina which allows access to the genital organs on the renal agenesis side d) Vaginal or complete cervico-vaginal unilateral agenesis, ipsilateral with the renal agenesis, and with no communication, or with communication between both hemiuteri (communicating uteri).
3. Isolated Müllerian anomalies affecting:	a) Müllerian ducts: they are the common uterine malformations as unicornuate (generally, with uterine rudimentary horn), bicornuate, septate and didelphys uterus b) Müllerian tubercle: cervico-vaginal atresia and segmentary anomalies such as transverse vaginal septum c) Both, Müllerian tubercle and ducts: (uni- or bilateral) Mayer-Rokitansky-Kuster-Hauser syndrome
4. Anomalies of the urogenital sinus:	cloacal anomalies and others.
5. Malformative combinations:	Wolffian, Müllerian and cloacal anomalies.

Anatomical variations and congenital anomalies of the uterine tubes

As mentioned above, the UTs play an essential role in fertilization by ensuring such important processes as the sperm transport, oocyte capture and transport, and early embryo development. Therefore, an abnormality of the UTs can result in impaired fertility or infertility. It is well known that anatomical variations and congenital anomalies of the uterine tubes (UTAVsCAs) are rare, and include such conditions as the paratubal hydatid cyst of Morgagni, accessory ostia, diverticula, complete or segmental agenesis, accessory UTs, undeveloped muscular layer, and failure in tube canalization [25,26]. Usually, the abnormalities are found accidentally during an investigation of infertility, pelvic surgery, Cesarean delivery, or at the time of laparoscopic sterilization. Until now, only a few case reports regarding UTAVsCAs have been published [27-30].

Agenesis of the UTs

Congenital agenesis of the UT could occur either due to a defect in the development of the Müllerian and mesonephric system, to a defect present in the region of the genital ridge and the caudal part of the paramesonephric Müllerian duct, or as a result of an ovarian pedicle torsion in birth, childhood or adult life. The absence of UT can be total – bilateral or unilateral (Fig. 2), or segmental – proximal (Fig. 3), mid-segmental (Fig. 4), or distal. Several case reports have been published of an incidental finding of bilateral or unilateral agenesis of the UTs. The first case was reported by Dannreuther in 1923 [31], followed by similar reports by Varino and Beacham (1941) [32] and Alexander (1947) [33]. The vast majority of patients with this anomaly are asymptomatic, therefore only laparoscopic, or laparotomic surgery due to other obstetric complications usually reveal the diagnosis (Table 2) [27,29,34-39].

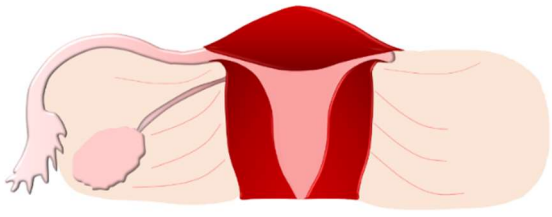

Fig. 2. Total unilateral agenesis.

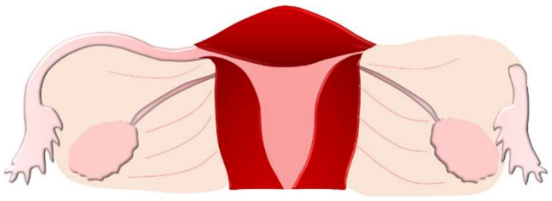

Fig. 3. Segmental (proximal) agenesis.

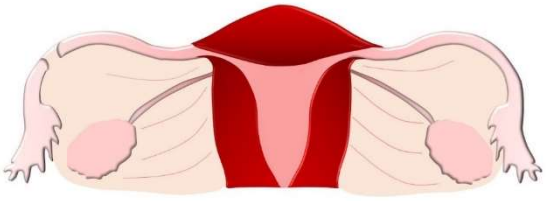

Fig. 4. Mid-segmental agenesis.

Table 2. Overview of selected case reports on bilateral/unilateral agenesis of the UTs.

Ref.	Number of patients	Age of patients	Tubal anomalies	Other urogenital anomalies	Symptoms	Fertility
Varino and Beacham (1941) *[32]*	1	27	Unilateral agenesis (left side)	Unicornuate uterus; Unilateral absence of ovary ureter and kidney	Pain in the lower abdomen; abnormal cervical discharge	Normal delivery (2x)
Alexander (1947) *[33]*	1	23	Unilateral agenesis (left side)	Unilateral absence of left ovary, left round and broad ligament, ureter, and kidney	Pain in the right lower quadrant of the abdomen; nausea and vomiting	Normal delivery (2x)
Chan and Leeton (1987) *[34]*	1	25	Bilateral agenesis	Bilateral absence of ovaries	Poorly developed secondary sex characteristics, amenorrhea	Infertility
Eustace (1992) *[27]*	2	1st patient - 24	Bilateral agenesis – blind 1cm endings	Cystic left ovary and absence of right ovary	Asymptomatic	Infertility
		2nd patient - 35	Unilateral agenesis (right side)	Absence of right ovary	Asymptomatic	Normal delivery (3x)
Gold et al. (1997) *[35]*	1	23	Bilateral agenesis	Bilateral absence of ovaries	Primary amenorrhea, hypoplastic breasts, genitalia, and uterus; estrogen deficiency	Infertility
Dahan et al. (2006) *[40]*	1	29	Partial unilateral agenesis – ampullary region (left side)	Congenital hydrosalpinx	Asymptomatic	Infertility
Muppala et al. (2008) *[41]*	1	22	Unilateral agenesis (right side)	Absence of right ovary and right kidney	Dyspareunia, dysmenorrhea, intermenstrual bleeding	NM
Uckuyu et al. (2009) *[42]*	2	1st patient - 26	Partial unilateral agenesis – part of the fimbria and distal ampullary segment (left side)	Streak left ovary	Asymptomatic	Infertility

		2nd patient - 36	Unilateral agenesis (right side)	Hydrosalpinx of the left uterine tube	Asymptomatic	Infertility
Pabuccu et al. (2011) *[36]*	1	21	Unilateral agenesis (left side)	Absence of left ovary	Asymptomatic	Infertility
Vaiarelli et al. (2012) *[37]*	1	31	Unilateral agenesis (right side) – 2 cm proximal stump	Absence of right ovary	Endometriosis; chronic pelvic pain	Infertility/ IVF ectopic pregnancy
Gursoy et al. (2013) *[38]*	1	46	Unilateral agenesis (left side)	Absence of left ovary and left kidney	Asymptomatic	Normal delivery (4x)
Tzitzimikas et al. (2013) *[43]*	1	19	Partial unilateral agenesis – distal segment (left side)	Absence of left ovary and ligaments	Acute pelvic pain due to right ovarian cyst rupture	NM
Chen et al. (2014) *[39]*	1	26	Unilateral agenesis (left side) – 2 cm tubal remnant	Absence of left ovary	Asymptomatic	Infertility
Agarwal et al. (2017) *[44]*	1	32	Partial unilateral agenesis – mid-tubal segment (left side) – 2 cm	No	Asymptomatic	Infertility
Alsina and Khamvongsa (2021) *[29]*	1	37	Unilateral agenesis (right side)	Absence of right ovary; polyhydramnios during elective Cesarean section	Asymptomatic	Spontaneous abortion, ectopic pregnancy
Gupta et al. (2018) *[45]*	1	10	Unilateral agenesis (left side)	Absence of left ovary; enlarged right ovary with torsion	Abdominal pain and vomiting	Premenarche
Mamah et al. (2022) *[46]*	1	36	Unilateral agenesis (left side)	Absence of left ovary and left kidney	Irregular vaginal bleeding	Ectopic pregnancy

For instance, Eustace [27] published two case reports regarding the absence of the UT. The first one was found in 24 years old healthy female with a normal hormone profile, who was examined due to a history of 3 years of primary infertility. Further examinations, such as hysterosalpingography, showed a normal uterine cavity with slightly dilatated proximal parts of the UTs. However, the laparoscopic procedure revealed 1 cm long blind remnants of both tubes. The second case was a 35-year-old female undergoing laparoscopic sterilization, during which was found 1 cm long blind remnant of the right tube arising from the right cornual region. Despite this anomaly, the patient had three normal vaginal deliveries. The author of this study hypothesized that such anomalies could be caused by the compressed blood supply of growing UTs during the 4th and 5th months of prenatal development, where the elongation and spiraling of tubes occur. Chen *et al.* [39] reported a case of unilateral left ovarian and uterine tube agenesis in a 26-years-old female admitted to a gynecology department for primary infertility. Diagnostic laparoscopy and hysteroscopy showed a 2-cm tubal remnant with the intact left round ligament, but interestingly at the same time, did not show any uterine or urinary tract malformations, which are often

associated with adnexal agenesis. On the other hand, the case of unilateral agenesis of the right ovary, UT, and round ligament, together with the agenesis of the right kidney, was found in a 22-years-old female. Surprisingly, the uterus was again unaffected. However, the patient presented symptoms such as dyspareunia, dysmenorrhea, and intermenstrual bleeding [41].

Dahan *et al.* [40] reported a partial absence of the ampullary portion and normal presence of the fimbriated section of the left UT in a 29-years-old female who had a two-year history of infertility. The patient was also diagnosed with congenital hydrosalpinx. It is known that the partial absence of the UT is often associated with an ipsilateral major uterus malformation, including a bicornuate uterus and renal anomalies; however, none of the mentioned pathologies were present in this patient. Two other cases with partial tubal agenesis were published by Uckuyu *et al.* [42]. The first one was a 26-years-old female diagnosed with primary infertility with the inability to conceive for 9 years. Performed ultrasonography (USG) and hysterosonography revealed a normal uterus, but the distal segment of the left tube was absent at diagnostic laparoscopy. The second case was a 36-year-old female with primary infertility. During laparoscopy, a short (2 cm) distal tubal fragment was found on the right side extending to the lateral pelvic wall. The distal tubal fragment was separated, and subsequent histopathologic examination showed inflammatory and degenerative changes in tubal tissue. As in the first case, the uterine cavity and tubal ostia were normal. Similarly, the emergency diagnostic laparoscopy due to a right ovarian cyst rupture in a 19-year-old female revealed agenesis of the distal part of the left UT, associated ligament, and ipsilateral ovary. There were no other uterine or renal abnormalities [43]. Another sporadic case of partial absence of the UT was published by Agarwal *et al.* (2017). A female patient, 32 years old, was examined due to primary infertility. Laparoscopy revealed normal ovaries and uterine cavity; however, at the cornual end of the left side was less than a one-centimeter stump, absent mid-tubal segment (2 cm), followed by normal infundibulum and fimbriated end. A fold of mesosalpinx connected two parts of the uterine tube [44]. Tandulwadkar *et al.* reported a case of bilateral agenesis of the medial part of the fimbriated end with hypoplastic fimbria and absence of the fimbria ovarica in a 27-year-old female who was laparoscopically examined due to primary infertility. The 3D USG revealed also bilateral hydrosalpinx and congenital complete uterine septum [47].

Recently, Alsina and Khamvongsa [29] published an incidental finding of congenital unilateral agenesis of the right ovary and right UT in a 37-year-old female patient during elective Cesarean delivery due to polyhydramnios. The patient had a history of recurrent spontaneous abortions and ectopic pregnancy; however, the routine USG showed no abnormalities during her obstetric care. Therefore, the authors pointed out the limitations of detecting the absence of UTs through imaging examinations, such as CT scans or USG, which often fail to visualize ovarian or tubal anomalies.

The most recent study published by Mamah *et al.* [46] presented a 36-years-old patient who underwent an emergency Cesarean section because of right tubal ectopic pregnancy. During the procedure, a complete absence of the left UT and ovary was found, but the uterus and right adnexa were normally developed. Four weeks later, performed renal USG displayed an absent left kidney. According to all findings, authors suggested that the cause of mentioned anomalies was left Müllerian agenesis, which also often comes with complications, such as ectopic pregnancy.

The vast majority of tubal agenesis cases is found in adult females; however, Gupta *et al.* [45]. published for the first time a case of a premenarchal girl at the age of 10 years who presented with acute abdominal pain and vomiting. The results from USG and MRI displayed right ovarian mass torsion, and subsequent laparoscopy revealed the absence of the left UT and ovary. At the same time, the uterus and urinary tract had normal size

Taken together, it is often stated that tubo-ovarian agenesis comes together with uterus anomalies and renal agenesis referring to a defect in Müllerian duct development or, more probably, to a defect in the genital ridge region. Nevertheless, according to our extensive case reports revision, in most of the studies, the uterus, as well as the urinary tract, were found completely normal. Therefore, the exact nature of such anomalies is still not entirely elucidated and needs further investigation.

Accessory UTs and/or duplication of the UTs

The accessory UT was firstly described in 1894 by Kossman [48], and it is characterized as a congenital anomaly caused by abnormal paramesonephric Müllerian duct development, specifically, the bifurcation of the cranial ends of the Müllerian ducts. The accessory UT is usually a cylindrical structure attached to the ampullary part of the normal UT (Fig. 5).

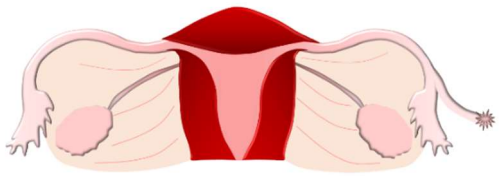

Fig. 5. Accessory UT attached to the ampulla of the normal UT.

They are a noteworthy factor contributing to infertility as their fimbria can pick the oocyte instead of normally developed UT fimbria. Other complications related to the presence of the accessory UT involve pyosalpinx, hydrosalpinx, cystic swelling, ectopic pregnancy, and torsion [28,49,50].

According to the extensive study published by Beyth and Kopolovic [51], who collected data from 200 abdominal surgeries performed on females, the estimated presence of the accessory UT is approximately 5 % to 6 %. Later on, Yablonski *et al.* [52] examined 100 fertile and infertile females aiming to identify the frequency of subtle tubal anatomical variations in both groups. As expected, the "infertile" group had more tubal/pelvic variations, from which the accessory UT accounted for 13 % of cases. Investigation of Coddington´s team of 100 surgical infertility patients and 398 surgical gynecology patients over six months revealed that five infertile patients had accessory UTs [49]. From that time, there has been no other more robust statistical information about the incidence of the accessory UT; however, there are numerous case reports describing mainly incidental findings of this anomaly (Table 3) [53-55].

Table 3. Selected case reports of accessory UTs.

Author of the case report	Number of patients	Age of patients	Tubal anomalies	Other urogenital anomalies	Symptoms	Fertility
Thonell et al. (1993) *[56]*	2	12 (both)	Acute accessory tube torsion on the right side (1st case) and on the left side (2nd case)	No	Right groin pain, nausea, diarrhea, and vomiting	Premenarche
Muzii et al. (2010) *[57]*	1	34	3 accessory tubes on the left side adnexa and 1 accessory tube on the right-side adnexa	No	Asymptomatic	Infertile
Gandhi et al., (2012) *[28]*	1	34	1 tortuous accessory tube attached to the ampullary portion of the right main tube	Enlarged polycystic right ovary	N/A	N/A
Uçar et al. (2017) *[58]*	1	30	2 accessory tubes attached to the ampullary portion of the right main tube	No	Asymptomatic	Fertile
Rottenstreich et al. (2016) *[53]*	1	16	Torsion of right accessory tube attached to the ampullary portion		Right lower quadrant abdominal pain and nausea due to ruptured ovarian cyst	Virgin
Duraisamy et al. (2020) *[54]*	1	14	1 accessory tube attached to the ampullary portion of the right main tube	Dermoid cyst on left ovary	Abdominal pain; moderate dysmenorrhea	Virgin
Kale (2021) *[55]*	2	1st patient 31	2 accessory tubes attached to the right and left main tubes	No	Asymptomatic	Fertile
		2nd patient 38	2 accessory tubes attached to the ampullary portion of the right main tube	No	Asymptomatic	Fertile

Beyth and Kopolovic [51] reported that all accessory UTs found during abdominal surgeries performed between June 1980 and December 1981 were attached to the ampullary segment of the UT and had their own fimbria. In any of these cases, no communication with the lumen of the main UT was observed. In 11 patients from 200, one accessory UT was found and one patient had even three of them. The authors further hypothesized that the accessory UTs or ostia might develop when one or more secondary invaginations of coelomic epithelium, which invaginated the Müllerian duct, fail to reach the lumen.

As mentioned above, one of the complications related to the presence of an accessory tube is ectopic pregnancy which was first observed by Groves in 1904 [59]. Another case of ectopic pregnancy, which needed to be solved by emergency surgery, was reported by Coddington *et al.* [49].

Gandhi *et al.* (2012) reported a finding of an accessory UT in a 34-years-old female cadaver during routine dissection for medical students. The accessory tube was attached to the ampullary portion of the right main UT with obliterated its lumen on the side of the attachment. They also found the right ovary to be enlarged and polycystic; however, the left UT and ovary had normal anatomy [28]. The presence of two accessory UTs in a 30-year-old female who underwent a Cesarean section was reported by Uçar *et al.* [58]. During the regular checking of the operating field, the authors found three tubes at the right adnexa. The two accessory tubes were thin and hypoplastic and arised from the ampullary segment of the main right UT. Both accessory tubes had developed fimbria; however, their lumens were obliterated at their mutual junction. As well as in the study mentioned above, the left adnexa and ovary were normal, and no renal abnormalities were observed. A very rare case of multiple accessory tubes was published by Muzii *et al.* [57]. Accessory tubes were found in a 34-year-old female who underwent diagnostic laparoscopy due to infertility lasting four years. In total, the surgery revealed six UTs. On the left side, four UTs were found, from which three were accessory tubes in different stages of hypoplasia and one was the normal main tube. On the right side was one accessory tube and one normal tube. Apart from that, the pelvic anatomy didn´t show any abnormalities.

Recently, Duraisamy *et al.* [54] reported a case of the right accessory tube present in a 14-year-old girl. A patient was examined due to persistent abdominal pain lasting three months and underwent USG and MRI, which both displayed a left ovarian dermoid cyst with no other pelvic abnormalities. During subsequent laparoscopic cystectomy, a small accessory tube with its own separate fimbria arising from the ampullary part of the right UT was found. In 1993, Thonell *et al.* [56] described two cases of premenarchal 12-year-old girls with symptoms of right groin pain, nausea, diarrhea, and vomiting. The surgical and subsequent pathological examinations showed that the reason for such symptoms was a complex cystic structure with elongated, fluid filled loops, lumen dilatation, and presence of fimbria, clearly referring to torsion of the accessory UT.

Most recently, Kale [55] described two interesting cases in which the presence of accessory UTs did not affect fertility. Both hypoplastic accessory tubes were found during a routine examination of the operating field and adnexa after the Cesarean section. The first patient was 31-years-old with two accessory UTs attached to both right and left main tubes, while the second 23-years-old patient had two accessory UTs attached to the right main tube.

All in all, the presence of an accessory UT is often mentioned as one of the possible causes of female infertility; however, there is a notable difference in available statistical information, and there are only several case reports describing the finding of this anomaly. For that reason, there is need for more robust clinical studies.

It is also important to note that this anomaly's terminology is misleading in some publications. Some authors termed the accessory UT as a duplication/or partial duplication of the UT, sometimes using both terms interchangeably throughout the publication [56,60-62]. On the other hand, Bergman's comprehensive encyclopedia of human anatomic variations [63] termed both the accessory and duplication of the UTs as supernumerary UTs. Compared, for instance, to gut malformations, there is a large category of intestinal duplications which are characterized as tubular structures connected to any part of the gut lined by the mucosa of the respective organ of their origin [64]. In the alimentary system, the term “accessory” is not used in the context of congenital anomalies, but is a name for digestive glands, and other digestion-associated organs like teeth. According to online medical dictionaries, the Free Dictionary by Farlex defines duplication as an abnormal doubling of a body part. After searching for “accessory”, the dictionary reads that accessory structures are either auxiliary and normally present, or they are supernumerary anomalies to another, larger structure or an organ of the same type. This

definition also states that "*accessory structures are duplication variations"* [65]. Compared to Stedman´s Medical Dictionary, it only mentions "duplicity" as a *"congenital malformation marked by duplication of one or more parts"*. On the other hand, "accessory" is defined as supernumerary, supplementary or adjuvant, perhaps referring to either congenital malformation (supernumerary) or normal auxiliary (supplementary) structure [66]. All in all, the terminology is obviously ambiguous and should be united for the sake of clarity when reporting case studies.

Accessory ostium of the UTs

Another developmental anomaly caused by the bifurcation of the distal end of the Müllerian ducts is the accessory ostium or secondary ostium, which is characterized by an ectopic fimbria located at a distance from the fimbriated end (Fig. 6).

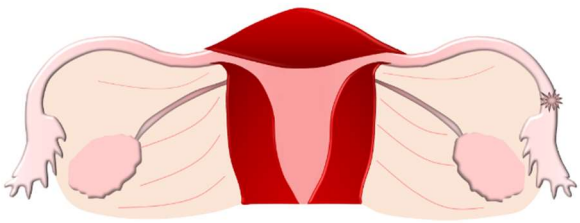

Fig. 6. Accessory ostium.

According to several studies, the prevalence of accessory ostia varies between 1.9 % to 10 % [52,62,67,68]. Accessory ostia whose distance from the normal fimbriated end is <1 are termed terminal ostia, and those distanced ≥ 1 cm are termed ampullary accessory ostia [26]. According to some case reports, the rare existence of accessory ostia contributes to the occurrence of infertility and possible endometriosis. The involvement of accessory ostia in infertility remains unclear; however, there is a hypothesis that ovulated oocyte may escape from the UT through the accessory ostium [68,69]. A close association between accessory ostia and endometriosis was proved by Zheng *et al.* [68] in their extensive retrospective analysis, in which the authors laparoscopically diagnosed the presence of accessory ostium in 21 of 1113 infertile patients (1.9 %); moreover, 19 patients out of those 21 were also diagnosed with endometriosis. In comparison, the accessory ostia were found in only 2 out of 710 patients without endometriosis. Likewise, Pereira and Klingman [69] reported a case of a 31-year-old female suffering from primary infertility. While hysterosalpingography and USG did not show any anomalies, the performed diagnostic laparoscopy revealed uterosacral endometriosis and accessory ostium at the right main UT. According to the above-mentioned reports, laparoscopic reconstructive surgery led, in many cases, to successful pregnancy outcomes.

Hydatid cyst of Morgagni

The hydatid cyst of Morgagni is a vestigial remnant of paramesonephric Müllerian duct or mesonephric Wolffian duct found near the fimbrial end of the UT as a pedunculated or sessile paratubal cyst (Fig. 7) [70].

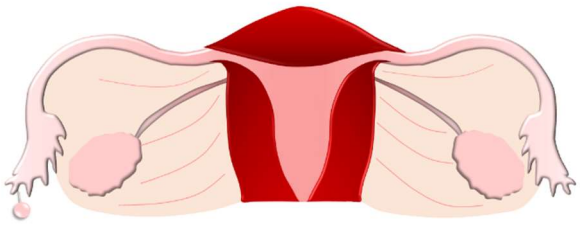

Fig. 7. Hydatid cyst of Morgagni.

They were described for the first time by an Italian anatomist Giovanni Battista Morgagni in 1761 and are often found incidentally during laparoscopic surgery, but their contribution to infertility is controversial. Nevertheless, few studies consider their possible impact on unexplained infertility [16,71,72]. Rasheed and Abdelmonem [16] conducted a non-randomized controlled trial aiming to evaluate the effect of the hydatid cyst of Morgagni on the pregnancy rate of infertile patients. During the four years (2006-2010), 1141 infertile females underwent laparoscopic surgery, whereas 409 were diagnosed with unexplained infertility, and 213 (52.1 %) of them were found to have hydatid cysts of Morgagni. In 127 of them, the cyst was removed laparoscopically (group 1), and the rest of the patients remained with no intervention (group 2). Most patients had unilateral cysts measuring from 1 to 2 centimeters located at the juxta-fimbrial portion of the UT. Subsequent follow-up observation and analyses revealed that the pregnancy rate of patients from group one (58.7 %) was significantly higher than that of patients in the second group (20.6 %). These results undoubtedly suggest that the cyst of Morgagni may considerably contribute to unexplained infertility. Likewise, Abd-el-Maeboud [73] considered the presence of paratubal cysts as a pathological factor hindering successful pregnancy achievement. In his case report, 3 patients with primary infertility underwent laparoscopy, whereas the only pelvic pathology found was

the hydatid cyst of Morgagni, which was removed during the surgery. Two of these patients were able to conceive spontaneously in the period of 2-3 months post-surgery. Based on the mentioned findings, diagnostic examination (transabdominal and transvaginal USG) of patients with unexplained infertility should also consider the hydatid cyst of Morgagni within differential diagnosis. Unfortunately, according to Barloon *et al.* [74], they are very difficult to diagnose before surgery, with the diagnostic success rate of only about 6.6 %.

Except for infertility, the presence of the hydatid cyst of Morgagni can also cause other urgent complications, such as its torsion or even torsion of the UT [14,75,76]. Rare cases involving torsion of the cyst of Morgagni in premenarchal girls were reported by Muthucumaru *et al.* [14]. Both 14 and 11-year-old patients suffered from an acute onset of right lower quadrant abdominal pain, due to which diagnostic laparoscopies were performed. It was expected that the cause of acute abdominal pain was appendicitis; nevertheless, surgical findings proved the presence of a contorted hydatid cyst with signs of acute hemorrhagic infarction.

Torsion of the UT caused by the presence of an extremely large hydatid cyst of Morgagni was published by Terzic *et al.* [76]. The authors described a case of a 19-year-old female who underwent an emergency laparotomy due to symptoms of an acute abdomen. A threefold twisted left UT with a large cyst measuring 10 centimeters in diameter was found during surgery. Authors suggested that such a big cyst was responsible for the tubal torsion because the UT with an attached cyst is much heavier, more mobile, and thus more prone to rotation.

Clinical significance

The clinical significance of uterine tube anatomical anomalies and congenital defects is often underestimated and neglected. As already mentioned, the MDAs usually focus only on the congenital anomalies of the uterus, and upper vagina. This can be partially explained by how rare these anomalies are. Although the MDAs in general are rare in their own right, the UTCAs are even more so. This is rooted in the embryonic development of paramesonephric ducts. The cranial parts develop into the future UTs in a much simpler manner compared to the caudal parts, which give rise to the uterus and upper vagina. These have to undergo a highly orchestrated and tightly regulated sequence of fusion and apoptosis in the midsection of the fused ducts, so there is more that can go wrong [77]. The MDAs including the UTCAs are most often diagnosed with imaging techniques like hysterosalpingography, pelvic ultrasound or magnetic resonance. The latter is the preferred approach thanks to its noninvasiveness, absence of radiation exposure, superior soft tissue visualization and capacity for multiplanar reconstruction [78]. The shortcomings of ultrasound imaging are reflected in the already cited Alsina and Khamvongsa [29] case report that found unilateral UT agenesis by chance during Cesarean section. Interestingly, in the history of the patient´s ultrasound examinations, no abnormal findings had ever been detected prior to the C-section [29]. Another problem can arise when a UTAVsCAs is confused with other anomaly, what can lead to the diagnosis of unexplained tubal infertility, while the true cause is merely undetected. For instance, a case study by Lelchuk *et. al.* [70] reported a patient with the diagnosis of appendiceal mucocele based on preoperative CT scan. Perioperatively, the authors found a mucinous mass near the ovary. Upon inspection, the consulted gynecologist concluded the finding as an ovarian cyst. Only after histopathological examination, it was revealed that the mass is in fact the paratubal hydatid cyst of Morgagni. This diagnostic confusion is clinically highly relevant since if left undiagnosed or misdiagnosed as other condition, it can lead to infertility that is categorized as idiopathic since its true cause is unrecognized [70].

Conclusions

Despite the rare occurrence, frequent absence of symptoms, accidental diagnosis, or clinical insignificance in some cases, UTAVsCAs are still a highly relevant topic. The first reason is that better understanding of any congenital anomaly broadens the bulk of knowledge of normal and anomalous embryonic development. This is significant, because these insights can be further translated to other clinically relevant and related fields of study like the investigation and management of other MDAs, e.g., the uterine anomalies. The second reason lies in the possibility of misdiagnoses that can result in unsubstantiated diagnoses like idiopathic infertility. It is true that the modern success of the whole field of reproductive medicine, especially the *in vitro* fertilization (IVF) techniques can deal with a wide spectrum of tubal factors of infertility. This is the reason why many researchers and clinicians think that UTs are no longer worth studying since they can be easily bypassed by IVF techniques. However, even the most state-of-the-art IVF technique

cannot fully reproduce the tubal microenvironment resulting in various complications, including the unsuccessful implantation of the transferred embryo. Any basic research on developmental anomalies or mature UTs has a great potential to enrich the clinical practice which is in the best interest of all infertile couples. Infertility has been rising globally, and this trend is estimated to go on with even worse numbers that we have to face today. We think that the view that studying UTs is not worth the effort is shortsighted with possible dire consequences in the future.

Conflict of Interest

There is no conflict of interest.

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