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REVIEW

Endometriosis in MRKH cases as a proof for the coelomic metaplasia hypothesis?

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Abstract

A diagnosis of endometriosis is based upon the histological identification of endometrial tissue at ectopic sites which are commonly located on the pelvic organs, the peritoneum and ovary. In rare cases, ectopic lesions can be found in other organs, such as kidney, bladder, lung or brain. Diagnosis is achieved by laparoscopic intervention followed by histological confirmation of endometriotic tissue. Prevalence is estimated at approximately 10% in the general female population with many patients experiencing pain and/or infertility. Currently, the implantation hypothesis by Sampson is the most accepted hypothesis about the pathogenesis of endometriosis. However, the occurrence of endometriosis in patients with Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome who sometimes lack a uterus or endometrium seems to suggest metaplasia as a cause of endometriosis. A critical reevaluation of the literature about MRKH does not reveal conclusive evidence of an association of uterus/endometrium agenesis and endometriosis. Most often only MRI diagnoses of uterus/endometrium agenesis and only very rarely conclusive histological evidence of the endometriotic lesions are presented. In contrast, whenever biopsies were performed endometriosis always appeared together with uterus/endometrium remnants. Taken together, we suggest that MRKH patients only develop endometriosis if a uterus/endometrium is present which underscores and not contradicts the implantation hypothesis of Sampson.

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Introduction

In its simplest definition endometriosis is a disease characterized by the presence of endometrial glands and stroma outside of the normal localization (Clement 2007). Furthermore, irrespective of location, endometriotic glands almost always have an overtly endometrioid appearance and histologically resemble uterine endometrial glands (Clement 2007). Despite this straightforward histological definition, it is puzzling that endometriosis and endometriotic lesions show so many different facets, such as variations in color, depth of invasion, adhesions, ovarian cysts and different epithelial-to-stromal cell ratios up to the extreme case of stromal endometriosis (Guo 2018).

Retrograde menstruation followed by implantation of the endometrial tissue on different surfaces in the pelvic or abdominal cavity is generally accepted as the main cause of endometriosis (Sampson 1927). Despite the high rate of retrograde menstruation, only approximately 10% of women in their reproductive age acquire endometriosis (Bulun 2009) pointing to secondary factors affecting the adhesion and invasion of endometrial cells thus resulting in endometriosis. It has been hypothesized that peritoneal endometriosis, endometriomas and deep-infiltrating endometriosis (DIE) could represent three distinct entities, which do not share a common pathogenesis (Nisolle & Donnez 1997). Especially ovarian endometriosis (endometriomas) was postulated to be derived from metaplasia (Zheng *et al.* 2005).

Robert Meyer (1924) was the first to introduce the hypothesis that endometriosis may arise from coelomic epithelium. The female reproductive tract develops from a pair of Müllerian ducts, which arise from coelomic epithelial cells of mesodermal origin (Kurita 2011; Fig. 1). Then the Müllerian ducts undergo a transformation from single tubes consisting of homogeneous epithelium and surrounding mesenchyme into several distinct organs, namely the oviduct, uterus, cervix and vagina. The underlying mesenchyme hereby dictates the organ-specific cell fate of the coelomic epithelium. However, we should keep in mind, that the ovaries only contain remnants from the coelomic epithelium in form of the mesothelial surface. In mature reproductive tracts, the developmental plasticity of coelomic epithelial cells is mostly lost (Kurita 2011; Fig. 1).

In endometriosis, the process of metaplasia is postulated to involve the transdifferentiation of a committed cell type (e.g. mesothelium) into an alternative cell type (e.g. endometrial epithelium). Recently,

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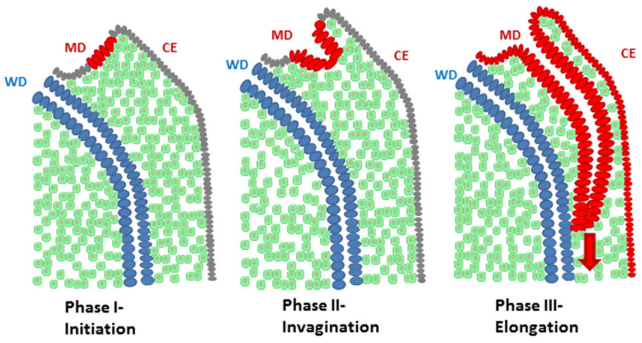

Figure 1 Development of the Müllerian duct (MD) and coelomic epithelium (CE). The MD arises as a local thickening (phase I) and CE invagination (phase II) at the cranial end of the urogenital ridge. The MD grows caudally (phase III, arrow) through the mesenchyme of the urogenital ridge and the tip comes into contact with the Wolffian duct (WD). The MD develops to the vagina (parts), cervix, uterus and oviduct; the CE develops to peritoneum and mesothelial surface cells (OSE) on the ovary.

metaplasia was also suggested for abdominal wall endometriosis (Ibrahim *et al.* 2017) and adenomyosis (García-Solares *et al.* 2018).

Methods

A search was carried out using Medline. Key words for the search were 'Mayer-Rokitansky-Kuster-Hauser' or 'MRK' in combination with 'uterus', 'endometrium' 'endometriosis', 'adenomyosis', 'metaplasia' in combination with 'MRKH', 'endometriosis' and 'adenomyosis' and 'ovarian metaplasia'. Each manuscript was downloaded and the histological evidences presented for the uterus, and eutopic and ectopic endometrium were evaluated. A summary of all reports dealing with MRKH together with endometriosis or adenomyosis can be found in Table 1.

Basic features of MRKH

The MRKH syndrome is named after August Franz Joseph Karl Mayer, Karl Freiherr von Rokitansky, Hermann Küster and Georges Andre Hauser; each of their observations have contributed to the discovery and definition of this disease (Patnaik *et al.* 2015). The incidence of MRKH is estimated to be 1 in 4000–5000 female newborns (Ledig & Wieacker 2018). Patients with MRKH typically have a normal ovarian function and a normal karyotype; however, a congenital aplasia of the vagina, cervix and uterus is often observed (Oppelt *et al.* 2012, Pan & Luo 2016, Wang *et al.* 2017). In the vast majority of cases primary amenorrhea leads to the initial presentation (Ledig & Wieacker 2018). MRKH is generally divided into two subtypes: MRKH type 1, in which only the upper vagina, cervix and uterus are affected, and MRKH type 2, which is associated with additional malformations affecting the renal and skeletal system (Londra *et al.* 2015). Most of the MRKH cases are sporadic, but analyses of the few reported familial cases suggest an autosomal-dominant inheritance with reduced penetrance (Ledig & Wieacker 2018). Up to date the etiology of MRKH is still unresolved (Rall *et al.* 2013, Ledig & Wieacker 2018). Although treatment options for MRKH are scarce (Londra *et al.* 2015), recently, treatment with a tissue-engineered vagina has gained some attention (Raya-Rivera *et al.* 2014).

Uterus and endometrium in MRKH patients

Several studies with large cohorts of MRKH cases showed that 48–99.2% MRKH patients still have a rudimentary uterus (Oppelt *et al.* 2012, Hall-Graggs *et al.* 2013, Marsh *et al.* 2013, Rall *et al.* 2013, Preibsch *et al.* 2014, Lalatta *et al.* 2015, Pan & Luo 2016, Wang *et al.* 2017). In three studies (Oppelt *et al.* 2012, Lalatta *et al.* 2015, Pan & Luo 2016) the numbers of aplastic uteri are not clearly specified. Most often magnetic resonance imaging (MRI) and ultrasound have been used to evaluate the presence of the uterus (Table 1). It is generally agreed that MRI is the modality of choice for further evaluation of all uterine anomalies (Londra *et al.* 2015). In a case series of MRKH patients ($n=214$) an overall correlation above 95% between MRI and laparoscopic findings was reported for 115 patients (Preibsch *et al.* 2014), which included 75% of patients with bilateral uterine rudiments, 15% with unilateral uterine rudiments and only 10% with complete uterine agenesis. In 85% of cases where uterine rudiments were removed, the presence of endometrial tissue was adequately diagnosed by MRI (Preibsch *et al.* 2014); however, 15% of endometria were missed by MRI.

Histological analysis from biopsies of MRKH patients demonstrated an endometrium in 40.5% (17/42; Rall *et al.* 2013), in 48% (23/48; Marsh *et al.* 2013) and in 100% (9/9; Wang *et al.* 2017) of the cases.

MRKH and endometriosis

In PubMed we searched for articles describing an association between MRKH and endometriosis. We identified 21 manuscripts, 19 of which were case reports (Table 1). Most of the authors identified MRKH by MRI and/or ultrasound and presented some evidence of endometriosis, especially of ovarian endometriosis and adenomyosis. Interestingly, in 7 out of 18 articles describing uterus remnants also endometria could be identified (Table 1). It remains unclear whether in the ten articles with uterine remnants, endometria were missed, because these assumptions were mostly based upon MRI or ultrasound. As shown in a comparative study, MRI detection of uterine remnants agreed in 77.3% with laparoscopy (Preibsch *et al.* 2014), thus demonstrating that MRI is not sufficient to prove the absence of uterus remnants. Additionally, the sensitivity of ultrasound in the detection of uterine remnants is even lower (Lermann *et al.* 2011).

Remarkably, in only 11 articles a biopsy of the uterus was undertaken and only three manuscripts presented histologic evidence of uterus/endometrium (Table 1). Furthermore, in only five articles histology of the endometriotic lesions was presented (Table 1). Enatsu *et al.* (2000) showed an endometrial/adenomyotic gland, but without an identifiable myometrium and the whole uterus not shown, the evaluation of adenomyosis is not conclusive (Fig. 2A, B and C). Furthermore

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Table 1 Findings of MRKH and endometriosis ordered chronologically.

Authors	CR or OR	Patients (*N*)	MRKH	Endometriosis	Uterus endometrium	Biopsy uterus	MRI	US	CT	Histology uterus	Histology lesion
Rosenfeld & Lecher (1981)	CR	1	Yes	Endometrioma	Uterine remnant	Done	n.d.	Done	n.d.	n.s.	n.s.
Acien (1986), Acien *et al.* (1988)	CR/CR	1	Yes	Tubal appendicular endometriosis, Endometrioma	Endometrium, uterine remnant	Done	n.d.	n.d.	n.d.	n.s.	n.s.
Mahboubi & Rostain (1987)	CR	1	Yes	Endometrioma	Uterine remnant	n.d.	n.d.	Done	Done	n.d.	n.d.
Malik *et al.* (1997)	CR	1	Yes	Adenomyosis, tubal endometriosis, Endometrioma	Endometrium, uterine remnant	Done	n.d.	Done	Done	n.s.	n.s.
Enatsu *et al.* (2000)	CR	1	Yes	Adenomyosis	Uterine remnant	Done	Done	n.d.	n.d.	Partly shown	Shown
Yan & Mok (2002)	CR	1	Yes	Adenomyosis	Uterine remnant	n.s.	n.d.	Done	Done	n.s.	n.s.
Sönmezer *et al.* (2003)	CR	1	Yes	Adenomyosis, endometrioma	Uterine remnant	n.d.	Done	Done	n.d.	n.s.	n.s.
Balci *et al.* (2008)	CR	1	Yes	Perirenal cyst	Agenesis	n.d.	n.d.	Done	n.d.	n.s.	n.s.
Cho *et al.* (2009)	CR	1	Yes	Endometrioma	Agenesis	n.d.	n.d.	Done	n.d.	n.s.	Shown
Doyle & Laufer (2009)	CR	2	Yes	One case with endometriosis, unspecified	Both with uterus remnants	Done	Done	n.d.	n.d.	n.s.	n.s.
Parkar & Kamau (2009)	CR	1	Yes	Endometrioma	Endometrium, uterine remnant	Done	n.d.	n.d.	n.d.	n.s.	n.s.
Mok-Lin *et al.* (2010)	CR	1	Yes	Posterior *cul-de-sac*	Possible uterine remnants	n.d.	Done	n.d.	n.d.	n.d.	n.s.
Yan *et al.* (2011)	CR	1	Yes	Endometrioma	Uterine remnant	n.d.	n.d.	Done	n.d.	n.d.	Shown
Elliott *et al.* (2011)	CR	1	Yes	Endometrioma	Endometrium, uterine remnant	Done	Done	Done	n.d.	n.s.	n.s.
Chun *et al.* (2013)	CR	1	Yes	Adenomyosis	Endometrium, uterine remnant	Done	Done	n.d.	n.d.	Shown	Shown
Marsh *et al.* (2013)	OR	48	Yes	5 unspecified cases	Endometrium, uterine remnant	Done	Done	n.d.	n.d.	n.s.	n.s.
Kawano *et al.* (2014)	CR	1	Yes	Endometrioma	Endometrium, myometrium	Done	Done	n.d.	n.d.	Shown	Shown
Troncon *et al.* (2014)	CR	1	Yes	Endometrioma	Uterine remnant	Done	Done	Done	n.d.	n.s.	n.s.
Hoo *et al.* (2016)	CR	1	Yes	Adenomyosis	Uterine remnant	n.s.	Done	n.d.	n.d.	n.s.	n.s.
Wang *et al.* (2017)	OR	92	Yes	Endometrioma	Uterine remnant	n.d.	Done	n.d.	n.d.	n.s.	n.s.

CR, case report; CT, computed tomography scan; MRI, magnetic resonance imaging; n.d., not done; n.s., not shown; OR, original research; US, ultrasound.

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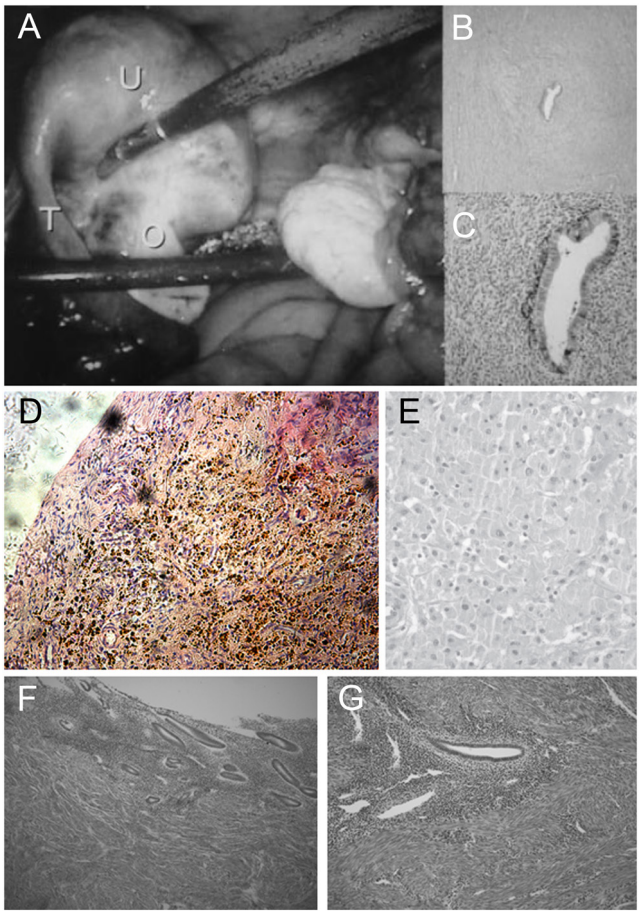

Figure 2 Photographs of MRKH cases associated with endometriosis. Enatsu *et al.* (2000) isolated from a laparoscopy (A) uterus remnants (B and C) and described the gland as adenomyosis. However, no myometrium is recognizable and the whole uterus is not shown. Yan *et al.* (2011) presented a case of ovarian endometriosis (D) of an MRKH patient; however, no cysts or glands are visible. Similarly, Cho *et al.* (2009) also showed a cyst of ovarian endometriosis (E) of an MRKH patient; however, no cyst is visible. In contrast, Chun *et al.* (2013) presented a normal endometrium (F) and an adenomyosis (G) of an MRKH patient.

the diagnosis of adenomyosis in MRKH patients is debatable because endometrial islands have been described as typical for MRKH patients (Ledig & Wieacker 2018).

In the figures presented by Yan *et al.* (2011; Fig. 2D) and Cho *et al.* (2009; Fig. 2E), no ovarian lesions are visible. Only Chun *et al.* (2013) presented histological evidence of endometrium and adenomyosis in one MRKH case (Fig. 2F and G). Marsh *et al.* (2013) observed in five MRKH patients an endometrium (100%) and reported also endometriosis, but did not describe the location. This was further substantiated by Will *et al.* (2013) with the same patient subgroup; however, histological evidence was again not presented. In contrast, despite a negative MRI for uterus remnants, Kawano *et al.* (2014) showed an endometrium, myometrium and an endometriotic cyst after laparoscopy.

Despite these shortcomings, most of the authors claimed to have proven endometriosis without uterus/endometrium

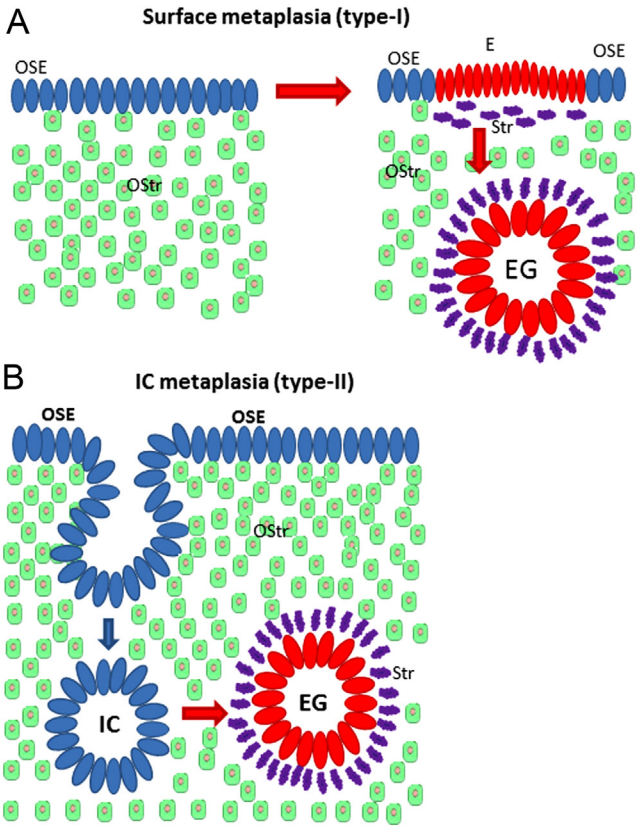

Figure 3 Scheme for ovarian metaplasia leading to endometriosis as proposed by Zheng *et al.* (2005). (A) OSE cells and the ovarian cortical stroma undergo metaplasia on the ovarian surface, which can result in endometrial glands in the ovarian stroma (OStr). (B) After invagination of the OSE and formation of an inclusion cyst (IC), metaplasia to an endometriotic gland (EG) occurs. E, ectopic endometrial epithel; EG, endometriotic gland; OSE, ovarian surface epithelium; OStr, ovarian stroma; Str, endometrial stroma.

in MRKH and thus suggested metaplasia as a possible cause of endometriosis (Enatsu *et al.* 2000, Yan & Mok 2002, Cho *et al.* 2009, Mok-Lin *et al.* 2010, Yan *et al.* 2011, Troncon *et al.* 2014, Hoo *et al.* 2016). However, none of the authors presented a hypothesis how metaplasia might happen.

Discussion

Metaplasia of ovarian epithelial and stromal cells?

Because in MRKH patients most often endometriomas were found, we will focus on the possibility of ovarian metaplasia. In a study about endometriomas, Zheng *et al.* (2005) categorized them as type 1 (or initial) when the endometriotic tissue was localized on the ovarian surface between ovarian surface epithelial (OSE) cells but can also form endometrial glands later on (Zheng *et al.* 2005; Fig. 2D in the reference). Endometrial glands forming inside the ovary after invagination of the OSE and subsequent formation of inclusion cysts were categorized as type 2 (Fig. 3). In addition to histology,

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they performed immunohistochemical analysis and found aromatase-positive epithelial/stromal cells and CD10-positive stromal cells in endometriomas type 1. They concluded that metaplasia did arise from transition of ovarian surface epithelial cells to endometrial epithelial cells and could be observed in endometriomas type 1 (Zheng *et al.* 2005). Although Zheng *et al.* (2005) mentioned metaplasia of the ovarian stromal components, no hypothesis was suggested whether the endometriotic stromal cells are generated from OSE or ovarian cortex cells. Recently, however, we could show that nearly all epithelial cells in all endometriomas were positive for keratin 18 and keratin 19 (Konrad *et al.* 2018*a*) a protein pattern that has never been found for ovarian surface epithelial cells. Thus, the transition of ovarian surface epithelial cells into endometrial epithelial cells seems highly unlikely as no intermediate cell types between OSE and endometriotic cells could be identified. Similarly, a transition of ovarian cortical or OSE cells to endometriotic stromal cells could not be observed (Konrad *et al.* 2018*b*).

Of note, Matsuura *et al.* (1999) used a coculture system of OSE and ovarian stromal cells in a 3D collagen lattice treated with 17β estradiol in which the OSE formed a lumen structure, surrounded by endometrial stromal cells with an epithelial mesenchymal structure. Immunohistochemistry with epithelial membrane antigen and cytokeratin was positive for the glandular cells, which also demonstrated tight junctions. Thus, Matsuura *et al.* (1999) suggested that endometriosis may manifest as a serial change from the adjacent mesothelial cells. Unfortunately the purity of the OSE by for example calretinin was not evaluated to exclude the possibility of contaminating tubal/endometrial epithelial cells. Furthermore the 'newly' formed endometrial stromal cells were not stained with CD10 to confirm endometriosis of at least the stromal cells.

Discussion of possible metaplasia models

Although very rarely mentioned, metaplasia of ovarian cells into endometriotic cells requires the differentiation into two distinct cell phenotypes, epithelium and stroma (Fig. 3). However, it still remains unclear whether this process starts from one cell type (e.g. mesothelium) or rather two cell types which then undergo metaplasia into two distinct cell types (stromal and epithelial). If we think about metaplasia of the mesothelium to generate ovarian endometriosis, rectovaginal cells to generate DIE or myometrial muscle cells (or other endometrial cell types) to generate adenomyosis, we have to postulate that in order to become endometrial stromal and endometrial epithelial cells very different cell types in very different surroundings must undergo the same 'endometrial metaplasia' program(s) whose initiating factor(s) are still unknown. Although such a scenario is highly unlikely, it was recently shown that approximately 17% of cortical ovarian inclusion cysts were paired boxed gene 8 (PAX8)- and calretinin double-positive. This points to metaplasia of calretinin-positive PAX8-negative inclusion cysts into PAX8/calretinin double-positive inclusion cysts (Park *et al.* 2018). Normally, OSE cells are calretinin -positive and PAX8 negative, whereas the secretory cells of the tubal fimbria are negative for calretinin and positive for PAX8. Although Park *et al.* (2018) did not analyze the surrounding stroma of the cortical inclusion cysts in detail, no obvious histological characteristics other than ovarian cortical stroma could be seen.

Although metaplasia as a cause of endometriosis is very often mentioned (Nisolle & Donnez 1997), only very rarely calretinin was used as a marker for peritoneal mesothelial cells or OSE to show metaplasia. To the best of our knowledge, we could identify only four manuscripts where endometriosis was immunohistochemically analyzed with calretinin, but none of them described a positive calretinin staining of endometriomas (McCluggage *et al.* 2003), liver cysts (Hsu *et al.* 2014), occult microscopic endometriosis in the peritoneum (Khan *et al.* 2014) or in a post-cesarean section scar (D'Agostino *et al.* 2019).

Conclusions

The best non-invasive choice for the diagnosis of MRKH is MRI, however, in up to 15% of cases uterus remnants are missed (Preibsch *et al.* 2014). Thus, in our opinion it is not sufficient to demonstrate uterus agenesis in MRKH patients (Balci *et al.* 2008, Cho *et al.* 2009) to be associated with endometriosis without confirmation by biopsy. Exceptional claims need exceptional evidences. We suggest that it is mandatory to present the histology of the uterus/endometrium remnants (if possible) and also from the endometriotic lesions to prove unequivocally uterus agenesis together with endometriosis; otherwise any conclusion of metaplasia is not substantiated. In cases of uncertainty the use of tissue biomarkers such as CD10 for stromal endometrial/endometriotic tissue (McCluggage *et al.* 2001) or other biomarkers such as calretinin for mesothelial cells (McCluggage *et al.* 2003) is indicated and conclusive histological pictures together with immunohistochemical evidence should be presented. As clearly shown in this manuscript the claim that the occurrence of endometriosis in MRKH patients is an indication of metaplasia and thus a counterargument to the implantation hypothesis by Sampson is not based on unequivocal proofs. Whenever uterine biopsies were performed endometriosis always appeared together with uterus/endometrium remnants in MRKH cases. Thus MRKH patients only develop endometriosis if a uterus/endometrium is present which underscores and not contradicts the implantation hypothesis by Sampson.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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