

Recent Developments on the Transmission of Human Life

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Berlin, Germany

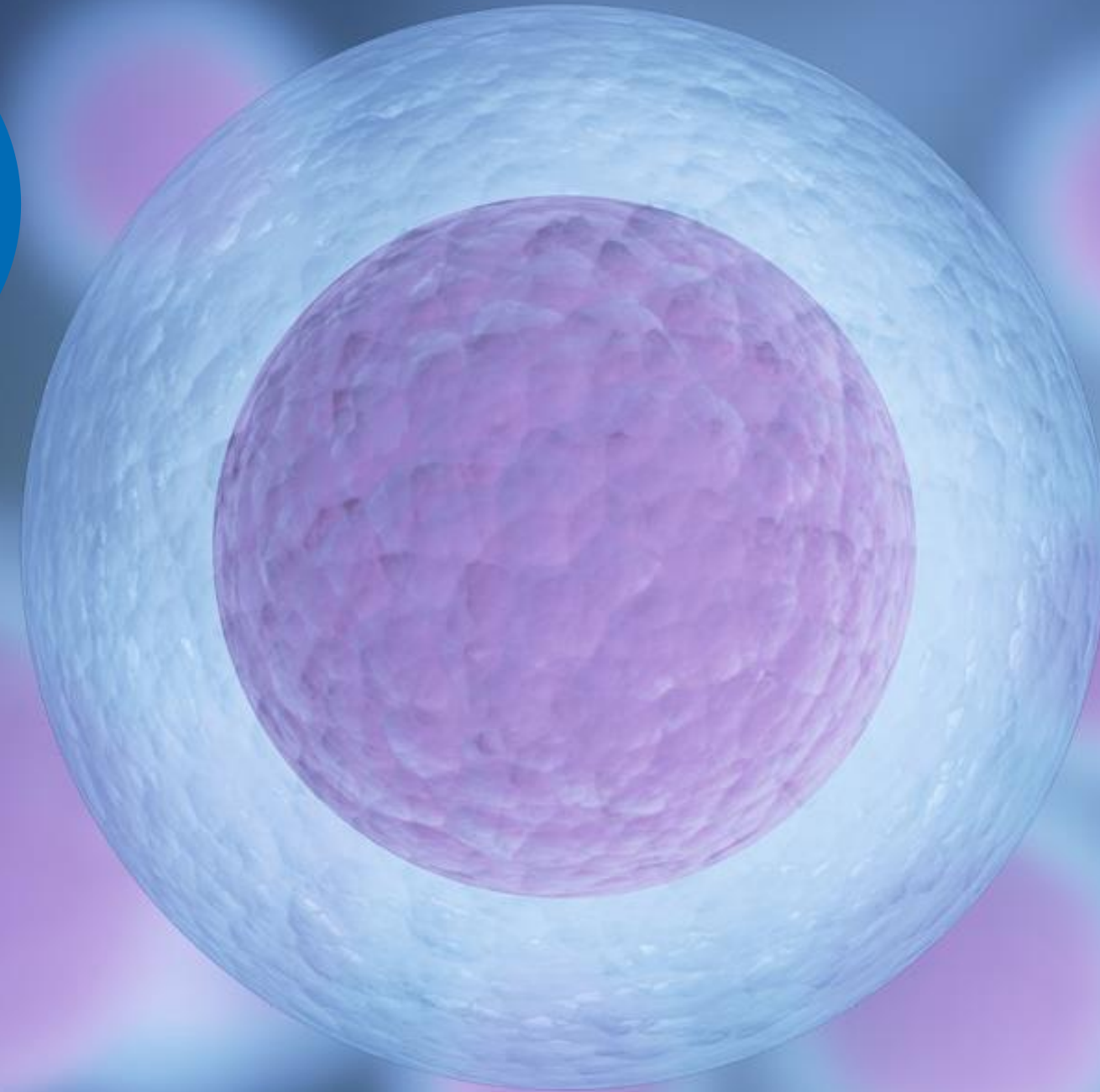
Welcome to all Participants



Recent Developments on the Transmission of Human Life

ABNORMAL UTERINE CAVITY ASSESSMENT,
CLASSIFICATION, AND TREATMENTS. WHAT
ARE EVIDENCE OF RESULTS?

Prof. Jan Bosteels



ABNORMAL UTERINE CAVITY ASSESSMENT, CLASSIFICATION, AND TREATMENTS. WHAT ARE EVIDENCE OF RESULTS?

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Faculty Disclosure

I have no potential conflict of interest to declare

LEARNING OBJECTIVES

- Reproductive implications of the different CUAs
- Strengths and weaknesses of the different classification systems of CUA
- Currently accepted indications for treating CUAs and their evidence base

CUA: PREVALENCE

Prevalence of CUA:

- Unselected population: 5.5%
- Infertility: 8.0%
- History of miscarriage: 13.3%
- Miscarriage + infertility: 24.5%

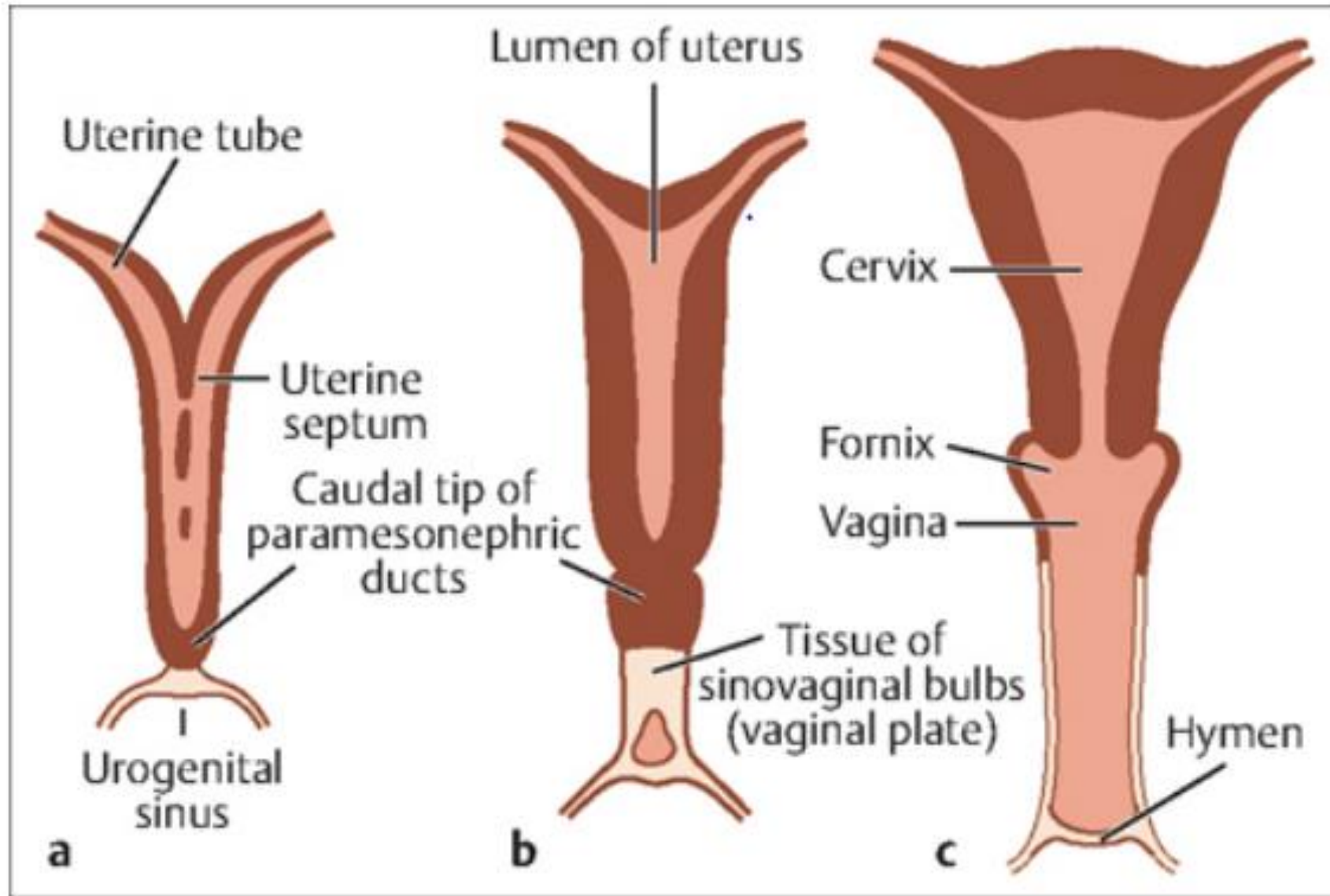
Chan et al. Hum Reprod Update 2011; 17: 761-71

CUA: THE UNCERTAINTY

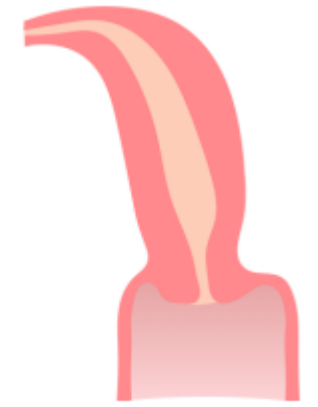
Issues of counseling/ care of ♀ with CUA:

- No universally accepted classification system
- Several tools to establish diagnosis
- Assessing the impact of CUA on reproductive potential of individual ♀ is difficult (clinical and methodological diversity of the studies in the literature)
- Gold standard = RCT (?) for studying the safety and effectiveness of surgical treatment of CUA. Only 1 study and its results and conclusions are not unanimously accepted by the professional community...

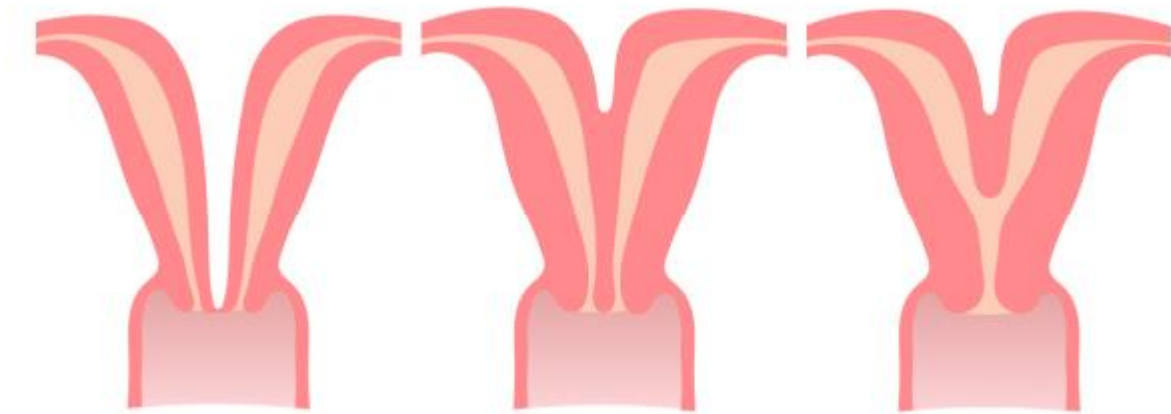
CUA: THE BASICS



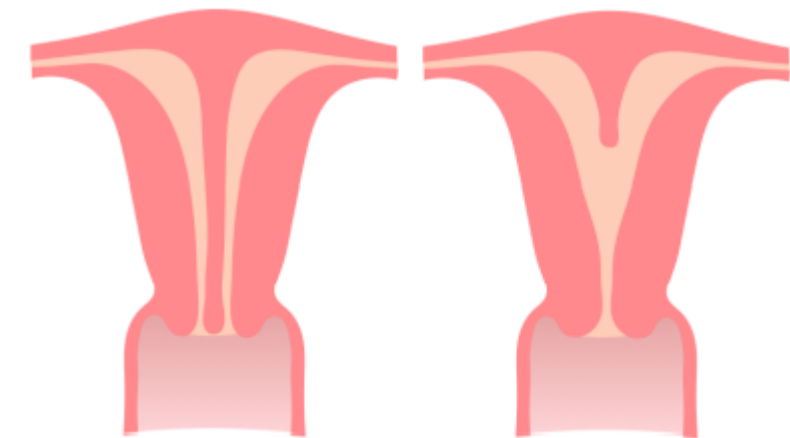
1. Formation of both Müllerian ducts



2. Fusion of Müllerian ducts



3. Resorption or canalisation



CUA: DIAGNOSIS

- Most ♀ with CUAs have no symptoms.
- The gold standard for definitive diagnosis was hysteroscopy +/- laparoscopy
- 2D TVUS and/or HSG are good for screening.
- 3D TVUS can accurately classify CUAs = new gold standard, less invasive.
- MRI is particularly useful for ♀ with unconfirmed diagnosis on 3D US or with complex CUAs.
- Mind associated (renal or other) anomalies!
- Conventional 2D US is minimally invasive, less expensive but operator dependent!

Marcal L, et al. Abdom Imaging 2011; 36: 756-64

Jayaprakasan K, et al. Ultrasound Obstet Gynecol 2011; 37: 727-32

Grimbizis G, et al. Hum Reprod 2016; 31: 2-7

Armstrong SC et al. Hum Reprod Update 2017; 23(5):533-547

CUA: REPRODUCTIVE IMPLICATIONS (1)

The majority of ♀ with CUAs have normal reproductive outcomes.

Very often the diagnosis of CUA is incidentally made during the exploration for subfertility, recurrent miscarriage or menstrual disorders.

CUAs with obstruction often present with pelvic pain.

MRKH syndrome or segmental hypoplasia: primary amenorrhea.

Jayaprakasan K, et al. Ultrasound Obstet Gynecol 2011; 37: 727-32

Reichman DE and Laufer MR. Best Pract Res Clin Obstet Gynaecol 2010; 193-208

Letterie GS. Reprod Biomed Online 2011; 23: 40-52

REPRODUCTIVE IMPLICATIONS (1)

- ♀ with **canalisation defects** have the poorest reproductive outcomes (SR 3805 ♀ with CUAs)

Conception rate	OR 0.86 (0.77-0.96)
First trimester miscarriage	OR 2.9 (2.0-4.1)
Preterm birth	OR 2.1 (1.5-3.1)
Fetal malpresentation at delivery	OR 6.2 (4.0-9.6)

REPRODUCTIVE IMPLICATIONS (2)

- ♀ with **fusion defects** do not have a reduced fertility (SR 3805 ♀ with CUAs)

	Bicornuate	Unicornuate	Didelphys
First trimester miscarriage	OR 3.4 (1.2-9.8)	OR 2.1 (1.1-4.5)	
Preterm birth	OR 2.5 (1.6-4.2)	OR 3.5 (1.9-6.2)	OR 3.6 (2.0-6.4)
Fetal malpresentation	OR 5.4 (3.1-9.2)	OR 2.7 (1.3-5.8)	OR 3.7 (2.0-6.7)

REPRODUCTIVE IMPLICATIONS (3)

- ♀ with a **dysmorphic uterus** (T-shaped or infantile uterus) reportedly have poor reproductive outcomes: there is an association with in utero exposure to DES^{1,2} but these studies are older.^{3,4} Due to 3D US recently more cases have been identified without a history of DES exposure- marginal IUAs or tuberculosis are also a possible cause.

1. The American Fertility Society. Fertil Steril 1988; 49: 944-55

2. Grimbizis G, et al. Hum Reprod 2013; 28(8): 2032-44

3. Berger MJ and Goldstein DP. Obstet Gynecol 1980; 55: 25-7

4. Herbst AL, et al. Am J Obstet Gynecol 1981; 141: 1019-28

HISTORICAL OVERVIEW CLASSIFICATION OF CUA

(Mid 19 th century	Cruveilher, Foerster & von Rokitansky)	
(1907	Strassman)	
1979	Buttram & Gibbons (AFS)	
1988	rAFS (ASRM)	
1992-2011	Acien & Acien embryological-clinical classification	
2005	VCUAM	
2013	ESHRE/ESGE	} objective 3D US measurements
2016	ASRM GL septum	
2018	CUME criteria	
2021	ASRM MAC 2021	

Oppelt P, et al. Fertil Steril 2005; 84(5): 1493-7

OVERVIEW OF CLASSIFICATION SYSTEMS

rAFS 1988 ¹	ASRM MAC 2021 ²	ESHRE/ESGE 2013 ³	VCUAM 2005 ⁴
I hypoplasia/agenesis	Müllerian agenesis	U0 nl uterus	V(agina) 0, 1a-b, 2a-b, 3, 4, 5a-b, S1-3, C, +, #
II unicornuate	Cervical agenesis	U1 dysmorphic uterus	C(ervix) 0, 1, 2a-b, +, #
III didelphys	Unicornuate	U2 septate uterus	U(terus) 0, 1a-c, 2, 3, 4a-b, +, #
IV bicornuate	Didelphys	U3 bicorporeal uterus	A(dnexa) 0, 1a-b, 2a-b, 3a-b, +, #
V septate	Bicornuate	U4 hemi uterus	M(alformation) 0, R, S, C, N, +, #
VI arcuate		U5 aplastic uterus	
VII DES drug related		U6 unclassified	
		C0-C4	
		V0-V4	

1. The American Fertility Society. Fertil Steril 1988; 49: 944-55

2. Pfeifer SM, et al. Fertil Steril 2021; 116(5): 1238-52

3. Grimbizis G, et al. Hum Reprod 2013; 28(8): 2032-44

4. Oppelt P, et al. Fertil Steril 2005; 84(5): 1493-7

CRITICISMS

- Lack of a comprehensive classification system able to classify all CUA, including the complex anomalies.
- Goal of the classification systems was to provide an easy to use and reliable reporting system (rAFS, ASRM MAC 2021) or to be comprehensive to include complex CUA (Acien 1992; Acien 2011). Combining both goals seems challenging...
- Not prospectively linked with reproductive outcomes.
- Link with management options would be helpful (ASRM MAC 2021)

MORE CLASSIFICATION, LESS CLARIFICATION

- Quantitative definitions used by the ESHRE/ESGE classification for septate uterus (U2) (internal indentation $\geq 50\%$ of the uterine wall thickness) and for bicorporeal uterus (U3) (external indentation $\geq 50\%$ of the uterine wall thickness) by 3-D US measurement have not been prospectively linked to reproductive outcomes.
- According to CUME group there is an overdiagnosis of septate uterus using the ESHRE/ESGE criteria compared to those of the ASRM classification (RR 14, 95% CI 5.9-33, $p \leq 0.01$). They have suggested a simple and reproducible definition of internal indentation of ≥ 10 mm to define a septate uterus.

Akthar MA, Saravelos SH, Li TC, Jayaprakasan K, on behalf of the RCOG. Reproductive Implications and Management of CUA. Scientific Impact Paper No 62. BJOG 2020; 127:e1-e13.

Ludwin M, et al. Ultrasound Obstet Gynecol 2018; 51: 101-9..

CUA: MANAGEMENT OPTIONS

- ♀ with complex CUAs require a multidisciplinary team for adequate management. Associated anomalies must be ruled out prior to any surgical intervention as these may impact on morbidity or quality of life
e.g. CUA + glomerulocystic kidney disease HNF-1 β 17q12 or AD 30-50% de novo, MURCS association (CUA, renal agenesis and hemivertebrae C5-D1).
- The general aim of adequate CUA management is to relieve symptoms such as pain in obstructive CUA and to avoid long-term health and reproductive adverse events.
- For non-obstructive CUAs the goal is to improve reproductive outcomes in infertile ♀ or ♀ with recurrent miscarriage.

MANAGEMENT OBSTRUCTIVE CUAS

- **Functioning rudimentary uterine horns**, often associated with unicornuate uterus need surgical removal to prevent the risk of hematometra or a pregnancy occurring in the rudimentary horn.
- **Obstructed hemivagina and ipsilateral renal anomaly** (OHVIRA, formerly Herlyn-Werner-Wunderlich Σ): resection of the longitudinal vaginal septum causing hematocolpos.

Gynecol Surg
DOI 10.1007/s10397-009-0469-3

COMMUNICATION

A case of didelphic uterus and blind hemivagina with renal dysplasia and ectopic ureter presenting with vulvodinia and recurrent fever

Elke Stevens • Jan Baekelandt • Lutgarde Lemmens •
Els Dufraimont • André Valcke • Marcel De Bruyn •
Jan Bosteels

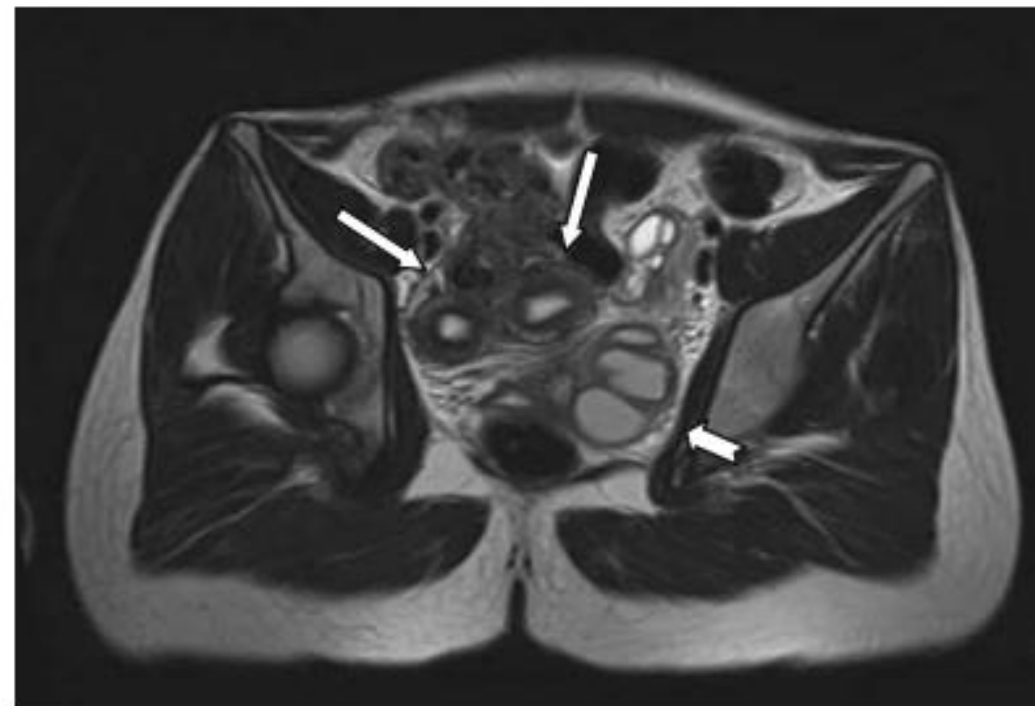


Fig. 1 MRI scan (paracoronaral T2-weighted image) showing the tortuous saccular dilated structure in the left hemipelvis (*thick arrow*) and the two uterine cavities (*thin arrows*)

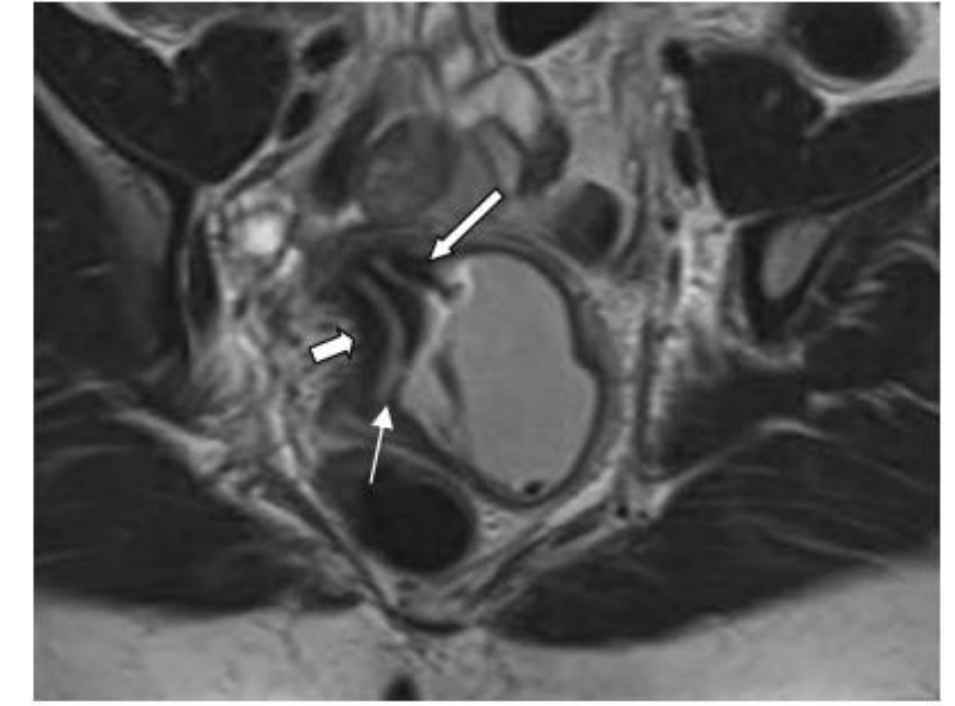


Fig. 2 MRI scan (paracoronaral T2-weighted image) before excision of the obstructive septum: left cervix (*long arrow*) draining into the blind hemivagina and right cervix (*short arrow*) draining to normal right hemivagina, with connection between the two hemitraits (*thin arrow*)

Stevens E, et al. Gynecol Surg 2010; 7:279-83

MANAGEMENT NON- OBSTRUCTIVE CUAS (1)

- Fusion defects** (uterus bicornis, uterus didelphys): abdominal metroplasty but higher risk of AE (prolonged hospital stay, longer recovery time, intraperitoneal adhesions, uterine rupture in subsequent pregnancy) and there is very limited low quality evidence on the effectiveness of abdominal metroplasty to improve reproductive outcomes (only 1 CCT in 21 ♀)

	Control-no surgery (N=13)	Intervention- abdominal metroplasty (N=8)
CPR 12 months	9/13 (67%)	5/8 (63%)
CPR 24 months	12/13 (95%)	7/8 (88%)
Probability of LB 1st pregnancy	30%	71%
Probability of LB 2nd pregnancy	58%	86%
Probability of LB 3rd pregnancy	79%	

Maneschi F, et al. Acta Eur Fertil 1993; 24: 17-20

MANAGEMENT NON- OBSTRUCTIVE CUAS (2)

1. Fusion defects
2. **Canalisation defects** (septate uterus): hysteroscopic metroplasty is often performed based on observational evidence suggesting better reproductive outcome following surgery.

SR + MA 25 studies: decreased risk for miscarriage RR 0.37 (95% CI 0.25-0.55) following surgery compared to no surgery but no differences between both groups for conception rates RR 1.1 (95% 0.79-1.6) or preterm delivery rates RR 0.66 (95% 0.29-1.5)¹

CR: no evidence for a benefit favoring hysteroscopic metroplasty vs expectant management in ♀ with recurrent miscarriage and septate uterus. *“As in the 2011 version of this review, we identified no RCTs for inclusion in this update”*²

1. Venetis CA, et al. *Reprod Biomed Online* 2014; 29: 665-83

2. Rikken JFW, Kowalik CR, Emanuel MH, Mol BWJ, van der Veen F, van Wely M, Goddijn M. Septum resection for women of reproductive age with a septate uterus. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD008576.

MANAGEMENT NON- OBSTRUCTIVE CUAS (3)

1. Fusion defects
2. **Canalisation defects** (uterus septus):

Only 1 RCT: The Randomised Uterine Septum Transsection Trial (TRUST)

- ❖ P women with uterine septum and child wish (history of recurrent miscarriage, subfertility or preterm birth)
 - ❖ I hysteroscopic resection of septum (n=39)
 - ❖ C expectant management (n=40)
 - ❖ O live birth rate
- ✓ ♀: 39% in I and 33% in C had infertility
- ✓ 92% ♀ in I and 90% ♀ in C had a partial uterine septum

Rikken JFW et al. Hum Reprod 2021; 36(5): 1260-1267

MANAGEMENT NON- OBSTRUCTIVE CUAS (4)

1. Fusion defects
2. **Canalisation defects** (uterus septus)

	Septum resection (n=39)	Expectant management (n=40)	Risk ratio (95% CI)
Live birth (n, %)	12 (31%)	14 (35%)	0.88 (0.47-1.7)
Ongoing pregnancy (n,%)	13 (33%)	14 (35%)	0.95 (0.52-1.8)
Clinical pregnancy (n, %)	22 (56%)	19 (48%)	1.2 (0.77-1.2)
Pregnancy loss (n,%)	11 (28%)	5 (13%)	2.3 (0.86-5.9)
Preterm birth (n, %)	5 (13%)	4 (10%)	1.3 (0.37-4.4)
			Hazard ratio (95% CI)
Cumulative LBR 12 m.			0.83 (0.39-1.86)

In ♀ with a partial uterine septum, hysteroscopic resection of the septum does not increase the chance of live birth.

Adapted from Rikken JFW et al. Hum Reprod 2021; 36(5): 1260-1267

HOW TO PROCEED FURTHER?

- In the absence of a universally accepted classification system, accurate 3D US measurements of external and internal indentations should be made and recorded in a large database. International professional societies should cooperate to gather 'big real life data' prospectively linking morphological anomalies to reproductive outcomes.
- MRI and combined hysteroscopy/laparoscopy should be reserved for diagnosing complex CUAs.

HOW TO INFORM OUR PATIENTS (1)

- The treatment of all cases of an **incidentally diagnosed septum in ♀ with infertility** is debatable and unproven.
- Consistent with the NICE recommendation hysteroscopic removal of a uterine septum can be offered in ♀ with **recurrent miscarriage** by a multidisciplinary team with adequate expertise and on the condition that appropriate clinical governance arrangements are made.
- **♀ with infertility and a septate uterus** should be informed that there is only one RCT that has demonstrated no benefit favoring surgery for improving reproductive outcomes. Treatment should only be offered in a research setting with special arrangements for clinical governance, consent and external audit.

HOW TO INFORM OUR PATIENTS (2)

- Future research agenda: multicentre RCTs assessing reproductive outcomes after hysteroscopic metroplasty in ♀ **with a septum and recurrent miscarriage or RIF following ART.**
- There is a lack of high-quality evidence to support abdominal or laparoscopic metroplasty in ♀ with CUAs with fusion defects.
- Some types of CUAs are associated with renal anomalies.
- Complex CUAs should be managed by a dedicated multidisciplinary team (gynaecologist, paediatrician, urologist, geneticist, psychotherapist, social worker,...).

HOW TO INFORM OUR PATIENTS (3)

- **♀ with CUAs** should be advised that they are at a higher risk for first and second trimester miscarriage, preterm labour, fetal malpresentation, IUGR and pre-eclampsia.
- **♀ with major fusion defects** are at high risk for placental insufficiency, IUGR and stillbirth (unilateral placental implantation→functional exclusion 1 UA?).
- **Pregnancies following successful surgical treatment in women with CUAs** are high-risk pregnancies and should be followed by a dedicated obstetrical team. Women at a high risk for preterm birth should be identified and managed by a dedicated team although it is currently not possible to draw firm conclusions regarding the screening and prevention of preterm labour in women with CUAs due to a lack of robust data.

Akthar MA, Saravelos SH, Li TC, Jayaprakasan K, on behalf of the RCOG. Reproductive Implications and Management of CUA. Scientific Impact Paper No 62. BJOG 2020; 127:e1-e13.

Take-home messages (1)

- ✓ There is a need for a universally accepted classification system prospectively linked to reproductive outcomes
- ✓ Recommendation against hysteroscopic metroplasty for an incidental septum in women with infertility.

Take-home messages (2)

- ✓ More research is needed in women with recurrent miscarriage or RIF after ART and a uterine septum.
- ✓ Pregnancies in women with CUAs (with or without treatment) are high-risk pregnancies and should be adequately managed.

THANK YOU



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