**UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA DE RIBEIRÃO PRETO**

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**Útero em forma de “T”: definição, critérios
diagnósticos, prevalência, implicações clínicas e
tratamento**

RIBEIRÃO PRETO

2020

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Tese apresentada à Faculdade de Medicina de
Ribeirão Preto da Universidade de São Paulo
para obtenção do título de Doutor em Ciências.

Área de Concentração: Ginecologia e
Obstetrícia.

**Orientador: Prof. Dr. Wellington
de Paula Martins**

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Resumo

Coelho Neto MA. **Útero em forma de “T”: definição, critérios diagnósticos, prevalência, implicações clínicas e tratamento.** Tese (Doutorado) - Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Ribeirão Preto. 2020.

Objetivos: Avaliar se existe medida confiável e precisa para distinguir o útero em “T” do útero normal/arqueado e sumarizar a evidência disponível em relação a definições, diagnóstico, prevalência, implicações clínicas e impacto do tratamento cirúrgico para o útero em “T” não relacionado ao dietilestilbestrol (DES). **Métodos:** Estudo prospectivo observacional para avaliar confiabilidade/concordância com elementos de acurácia diagnóstica em uma amostra de 100 blocos de ultrassonografia tridimensional (US-3D) de úteros apresentando endentaço lateral da cavidade, tendo como padrão de referência a impressão subjetiva de 15 especialistas. As medidas foram realizadas de forma independente por dois especialistas para avaliar o coeficiente de correlação de concordância (CCC), a precisão diagnstica pela área sob a curva (AUROC), e o melhor ponto de corte pelo índice de Youden. Para resumir a evidncia disponvel em relao ao tero em “T”, realizou-se uma reviso sistematizada buscando estudos no *PubMed*, *Scopus* e EMBASE em mar-2020. Estudos sobre tero em “T” no relacionado ao DES incluindo 10 ou mais mulheres foram elegveis. **Resultados:** No estudo de reprodutibilidade e preciso diagnstica, foram includos 100 participantes (pelo padro de referncia, 20 foram julgados em “T” e 80 normais/arqueados). A concordncia entre especialistas foi de 82% ($\kappa=0,43$). As trs medidas identificadas com preciso diagnstica e seus respectivos pontos de corte foram: ngulo de endentao lateral ($\text{AUROC}=0,95$) $\leq 130^\circ$, profundidade da endentao lateral ($\text{AUROC}=0,92$) ≥ 7 mm, e ngulo “T” ($\text{AUROC}=0,87$) $\leq 40^\circ$. O ngulo “T” foi a medida com melhor reprodutibilidade interobservador ($\text{CCC}=0,87$). Sugere-se considerar tero em “T” na presena dos trs critrios (valor preditivo positivo=0.93). Na reviso sistematizada, 2504 referncias foram identificadas, e 20 estudos foram includos. H apenas estudos de baixa qualidade. O diagnstico do tero em “T” foi, comumente, realizado por US-3D, e o critrio mais citado foi o da European Society of Human Reproduction and Embryology and the European Society for Gynecological Endoscopy (ESHRE-ESGE). A prevalncia do tero em “T” variou de 0,2-10%. Sua etiologia foi relacionada adenomiose, sinquias e como sendo uma condio primria. Resultados reprodutivos ruins foram relacionados ao tero em “T” (infertilidade, aborto, parto pr-termo, gravidez ectpica e falha de implantao). Os benefcios do tratamento cirrgico por metroplastia histeroscpica foram analisados em 12 estudos, que mencionaram melhora nas taxas de gravidez, nascidos vivos, parto a termo, reduo de abortamento e gravidez ectpica (evidncia de muito baixa qualidade). **Concluses:** A concordncia entre especialistas para o diagnstico do tero em “T” foi moderada. Trs medidas tiveram boa acurcia diagnstica e confiabilidade razovel a moderada. At o momento, prevalncia, importncia clnica e impacto da cirurgia nos resultados reprodutivos de mulheres com tero em “T” so desconhecidos. Alguns estudos relatam melhora nos resultados reprodutivos aps a cirurgia, mas a evidncia de muito baixa qualidade. A definio proposta pelo CUME para tero em “T” poder ajudar no desenvolvimento de ensaios clnicos randomizados e ser adotada pelas diretrizes no estudo das malformaes uterinas.

Palavras-chave: Ductos mllerianos. Anormalidades do tero. tero em “T”. Concordncia no tero dismrfico. Endentao lateral. Dietilestilbestrol.

Abstract

Coelho Neto MA. **T-shaped uterus: T-shaped uterus: definition, diagnostic criteria, prevalence, clinical implications, and treatment.** Tese (Doutorado) - Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Ribeirão Preto. 2020.

Objectives: To assess whether is there any uterine measurement that is reliable to distinguish between T-shaped and normal/arcuate uterus and to summarize the current evidence regarding definitions, diagnosis, prevalence, clinical implications and impact of surgical treatment for T-shaped uterus not related to Diethylstilbestrol (DES) exposure. **Methods:** A prospectively designed multi-rater reliability/agreement study with elements of diagnostic accuracy study was performed in a sample of 100 three-dimensional (3D) datasets of uteri presenting lateral uterine cavity indentation, using as reference standard the subjective impression of fifteen blinded experts. The measurements were independently performed by two blinded experienced observers to evaluate the concordance correlation coefficient (CCC), the diagnostic test accuracy by the area under ROC curve (AUROC) and the best cut-off value by using Youden's index. To summarize the available evidence regarding T-shaped uterus, we have performed a systematic review searching on *PubMed*, *Scopus* and *EMBASE* on Mar-2020. All studies presenting any data regarding T-shaped uterus not related to DES exposure including at least 10 women were eligible. **Results:** In the reliability and accuracy study, we have included 100 participants (20 T-shaped uteri and 80 normal/arcuate in the reference standard). The agreement among experts was 82% ($\kappa = 0.43$). Three measurements with good diagnostic test accuracy were identified and their respective cut-offs were: lateral indentation angle ($\text{AUROC}=0.95$) $\leq 130^\circ$, lateral indentation depth ($\text{AUROC}=0.92$) ≥ 7 mm, and T-angle ($\text{AUROC}=0.87$) $\leq 40^\circ$. T-angle was the one with the best inter-observer reproducibility ($\text{CCC}=0.87$). We suggest considering as T-shaped uterus when meeting all the three criteria (positive predictive value=93). In the systematic review, 2,504 records were found, and 20 studies were included. There are only poor-quality studies. The diagnosis of T-shaped uterus was most based in three-dimensional US (3D-US) and the most cited was the criteria from European Society of Human Reproduction and Embryology and the European Society for Gynecological Endoscopy (ESHRE/ESGE). The prevalence of T-shaped uterus varied from 0.2-10%. The etiology of T-shaped uterus was assigned to adenomyosis, adhesions and as a primary condition. Worse reproductive outcomes were related to T-shaped uterus (infertility, miscarriage, preterm delivery, ectopic pregnancy, and repeated implantation failure). The benefits of surgical treatment by hysteroscopic metroplasty were analyzed by 12 studies, which had mentioned improvement on pregnancy, live birth and term delivery rates, reduction in miscarriage and ectopic pregnancy (evidence of very low quality). **Conclusions:** The agreement among top-experts for diagnosing T-shaped uterus was moderate. Three measurements had good diagnostic test accuracy and fair to moderate reliability. Until now, prevalence, clinical relevance, and impact of surgery on reproductive outcomes in women with T-shaped uterus are unknown. Some studies report improvement on reproductive outcomes after surgery, but the evidence is of very low quality. The CUME definition of T-shaped uterus may help with the development of interventional randomized controlled trials and therefore could be adopted by guidelines on uterine anomalies.

Keywords: Mullerian ducts. Congenital uterine anomalies. T-shaped uterus. Dysmorphic uterus agreement. Lateral indentation. Diethylstilbestrol.

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Lista de Abreviaturas

AFS-	<i>American Fertility Society</i>
ASRM-	<i>American Society for Reproductive Medicine</i>
CUME-	Malformações uterinas congênitas por especialistas
DES-	Dietilestilbestrol
ECR-	Ensaio clínico randomizado
ESHRE-ESGE-	<i>European Society of Human Reproduction and Embryology- European Society for Gynecological Endoscopy</i>
US-3D-	Ultrassonografia tridimensional

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1- Introdução

O útero em “T” é uma malformação uterina congênita consequente à falha no desenvolvimento tardio do útero (útero hipoplásico, útero em “T” e exposição ao dietilestilbestrol (DES) (1). O útero em “T” exhibe endentaço lateral com estreitamento importante da cavidade uterina nas paredes laterais (2), o que faz com que o formato da cavidade endometrial lembre a letra “T” (3).

O útero em “T” foi primeiramente mencionado por Kauffman et al. (4), por Buttran e Gibbons (5) e pela *American Fertility Society* (AFS) (agora denominada *American Society for Reproductive Medicine* - ASRM) (6), como um defeito relacionado à exposio ao DES, sem meno de critrios para definir esta condio (defeitos do tipo VII ou relacionados ao DES). Em 2013, a *European Society of Human Reproduction and Embryology* e a *European Society for Gynecological Endoscopy* (ESHRE-ESGE) propuseram uma definio para útero em “T” que consiste na presena de cavidade uterina estreita devido ao espessamento das paredes laterais com correlao 2/3 do corpo uterino e 1/3 do colo do útero (2), na qual no so mencionados critrios objetivos para diagnosticar o útero em forma de “T” e nem como as medidas do útero seriam realizadas.

Em 2016, o ESHRE-ESGE props um consenso atualizado sobre o diagnstico de malformaes uterinas (7). Sugere-se que em uma imagem de US-3D (ultrassonografia tridimensional) renderizada, as medidas sejam realizadas no plano mdio-coronal do útero. O US-3D, alm de ser uma tcnica no invasiva, bem tolerada pelas pacientes e ter baixo custo (8,9), permite a visualizao do plano coronal do útero, criado por reconstruo volumtrica, possibilitando viso frontal do útero, detalhes da cavidade uterina e contorno externo do útero (9). Os blocos de US-3D podem ser armazenados para anlise *off-line* posterior (10). Sugere-se medir a espessura da parede uterina como a distncia entre a linha que conecta os dois stios tubrios e o contorno uterino externo em casos de pacientes com superfcie uterina externa normal. A espessura da parede lateral estimada medindo-a no ngulo de 90 em relao ao revestimento da juno endometrial-miometrial (7). No so mencionados valores absolutos a serem usados para identificar teros em forma de “T”.

A ASRM tambm desenvolveu um novo protocolo em 2016 (11), em que reconhecida a importncia de se diferenciar o útero septado do útero arqueado;

porém nada menciona em relação ao útero em forma de “T”. De acordo com esta diretriz, um número considerável de úteros permanece sem classificação, e pacientes permanecem não diagnosticadas.

O primeiro estudo CUME (malformações uterinas congênitas por especialistas) (12) foi publicado com o objetivo de avaliar o nível de concordância entre os especialistas em distinguir entre útero septado e útero normal/arqueado aplicando avaliação subjetiva de imagens no plano coronal do útero por meio de US-3D. Além disso, forneceu critérios mais precisos para diferenciar o útero septado do útero normal/arqueado. Embora essa classificação tenha alcançado melhor entendimento na diferenciação do útero normal/arqueado em relação ao septado, ela não menciona o útero em forma de “T”.

O útero em forma de “T” é comumente relacionado à exposição *in utero* ao DES (6,13), um medicamento prescrito para gestantes em diferentes países para evitar abortos até a década de 1980 (14). As últimas dentre as 1-1,5 milhão de mulheres expostas ao DES intraútero não estão mais em idade reprodutiva (15,16), mas o útero em “T” continua a ser identificado em mulheres jovens (3,17). A patogênese do útero em forma de “T” não é clara, e a etiologia, em muitos casos, é desconhecida (3,13). O útero em “T” também pode ser de origem primária (18-20), decorrer de aderências na síndrome de Asherman (3,13,18,20,21) ou adenomiose (22). Seu diagnóstico deve se basear, exclusivamente, na forma da cavidade uterina por técnicas de imagem, sem vincular o diagnóstico a uma etiologia identificada (como ocorreu na classificação da AFS, que relacionava útero em “T” ao DES) (6).

A prevalência de defeitos uterinos na população geral/fértil é de aproximadamente 7% (23). No entanto, mulheres que apresentam malformações uterinas podem ter maior comprometimento da saúde reprodutiva (7). Os defeitos uterinos podem ser encontrados em 8% das mulheres inférteis, 13% daquelas que sofrem abortos recorrentes e 24% das que apresentam as duas condições (24). A prevalência do útero em forma de “T” não é conhecida (24), por não haver consenso sobre sua definição, nem uniformidade nos métodos empregados para diagnósticos nos estudos realizados até o momento (25), além da subjetividade na definição do ESHRE/ESGE (2), a mais utilizada. Ademais, os estudos disponíveis até o momento sobre o útero em “T” incluem apenas mulheres com antecedentes de resultados

reprodutivos ruins: infertilidade (13,26,27), abortamento (20,21,26-28), aborto de repetição (20,21,26-28), parto pré-termo (29,30), falha de implantação (20,21,27-29,31) e gravidez ectópica (29). Não há dados referentes a desfechos reprodutivos do útero em “T” na população geral; não se sabe, portanto, quantas mulheres conseguem alcançar gravidez bem-sucedida apesar de ter útero em “T”, pois elas não chegam aos serviços de medicina reprodutiva.

O recente interesse pelo útero em “T”, e o crescente número de estudos sugerindo melhora nos resultados reprodutivos de mulheres com útero em “T” após metroplastia histeroscópica (3,13,32-35) podem ser decorrentes do aumento do diagnóstico dessa condição devido à definição proposta pelo ESHRE-ESGE de anomalias uterinas congênitas (36,37), com o risco de operar pacientes com útero normal (25,38). Não existe evidência robusta para oferecer o tratamento cirúrgico na prática clínica (25). Estudos randomizados com grupo controle de pacientes não tratadas são necessários para se avaliar melhor a eficácia da intervenção cirúrgica nos desfechos reprodutivos (3,32,34).

O principal desafio no estudo do útero em “T” é a ausência de critérios mensuráveis, e isto é uma barreira importante na construção de evidência em relação a prevalência, implicações clínicas e manejo desta condição. Apenas com critérios diagnósticos objetivos e mensuráveis será possível investigar se mulheres com útero em “T” obtêm piores desfechos reprodutivos e, então, avaliar a necessidade de realização de ensaios clínicos controlados para investigar o benefício do tratamento cirúrgico desta condição nos desfechos reprodutivos.

2. Objetivos

2.1 Objetivos gerais

Avaliar se existem critérios diagnósticos mensuráveis confiáveis e precisos para distinguir o útero em forma de “T” do útero normal/arqueado, tomando como referência o diagnóstico feito, com mais frequência, por múltiplos especialistas (por meio de imagens de US-3D no plano coronal), e sumarizar a evidência disponível para o útero em forma de “T” não relacionado à exposição ao DES sobre definições, diagnóstico, prevalência, implicações clínicas e impacto do tratamento cirúrgico nos desfechos reprodutivos.

2.2 Objetivos específicos

- Avaliar a confiabilidade/concordância interobservador de medidas e estabelecer critérios diagnósticos objetivos para o útero em “T”, além de distinguir o útero em “T” do útero normal/arqueado.
- Analisar a precisão diagnóstica e os melhores pontos de corte para as medidas propostas.
- Definir o útero em “T” utilizando critérios mensuráveis objetivos, precisos e confiáveis.
- Identificar o método diagnóstico mais citado nos estudos sobre útero em “T”.
- Avaliar o critério diagnóstico mais comumente utilizado no estudo do útero em “T”.
- Estimar a prevalência do útero em forma de “T”.
- Listar possíveis etiologias relacionadas ao útero em “T” não associadas à exposição ao DES.
- Compreender as implicações clínicas do útero em “T” nos desfechos reprodutivos.
- Analisar a evidência disponível sobre o tratamento cirúrgico do útero em forma de “T”.

3. Artigos

**Artigo 1: Congenital Uterine Malformation by Experts
(CUME): T-shaped uterus**

Congenital Uterine Malformation by Experts (CUME): diagnostic criteria for T-shaped uterus

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CONTRIBUTION

What are the novel findings of this work?

The prevalence, clinical relevance and appropriateness of management of T-shaped uterus is not fully understood, due to the lack of objective criteria for its diagnosis. This study developed an objective definition of T-shaped uterus based on the diagnosis made most often by representative expert clinicians, surgeons and sonologists. We identified three uterine morphometric measurements in the coronal plane, with cut-offs (lateral internal indentation depth ≥ 7 mm, lateral indentation angle $\leq 130^\circ$ and T-angle $\leq 40^\circ$) that have good diagnostic test accuracy and fair-to-moderate reliability for the diagnosis of T-shaped uterus.

What are the clinical implications of this work?

These three measurements, with cut-offs, can be used to confirm the diagnosis when there is suspicion of T-shaped uterus on subjective assessment of the uterine cavity. When these CUME definitions and criteria are used, doctors and patients can be confident that the diagnosis

of T-shaped uterus has high probability of being correct. Using these criteria will allow elucidation in future studies of the prevalence, clinical relevance and management of T-shaped uterus.

ABSTRACT

Objectives To identify uterine measurements that are reliable and accurate to distinguish between T-shaped and normal/arcuate uterus, and define T-shaped uterus, using Congenital Uterine Malformation by Experts (CUME) methodology, which uses as reference standard the decision made most often by several independent experts.

Methods This was a prospectively planned multirater reliability/agreement and diagnostic accuracy study, performed between November 2017 and December 2018, using a sample of 100 three-dimensional (3D) datasets of different uteri with lateral uterine cavity indentations, acquired from consecutive women between 2014 and 2016. Fifteen representative experts (five clinicians, five

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surgeons and five sonologists), blinded to each others' opinions, examined anonymized images of the coronal plane of each uterus and provided their independent opinion as to whether it was T-shaped or normal/arcuate; this formed the basis of the CUME reference standard, with the decision made most often (i.e. that chosen by eight or more of the 15 experts) for each uterus being considered the correct diagnosis for that uterus. Two other experienced observers, also blinded to the opinions of the other experts, then performed independently 15 sonographic measurements, using the original 3D datasets of each uterus. Agreement between the diagnoses made by the 15 experts was assessed using kappa and percent agreement. The interobserver reliability of measurements was assessed using the concordance correlation coefficient (CCC). The diagnostic test accuracy was assessed using the area under the receiver-operating-characteristics curve (AUC) and the best cut-off value was assessed by calculating Youden's index, according to the CUME reference standard. Sensitivity, specificity, negative and positive likelihood ratios (LR- and LR+) and post-test probability were calculated.

Results According to the CUME reference standard, there were 20 T-shaped and 80 normal/arcuate uteri. Individual experts recognized between 5 and 35 (median, 19) T-shaped uteri on subjective judgment. The agreement among experts was 82% (kappa = 0.43). Three of the 15 sonographic measurements were identified as having good diagnostic test accuracy, according to the CUME reference standard: lateral indentation angle (AUC = 0.95), lateral internal indentation depth (AUC = 0.92) and T-angle (AUC = 0.87). Of these, T-angle had the best inter-observer reproducibility (CCC = 0.87 vs 0.82 vs 0.62 for T-angle vs lateral indentation depth vs lateral indentation angle). The best cut-off values for these measurements were: lateral indentation angle $\leq 130^\circ$ (sensitivity, 80%; specificity, 96%; LR+, 21.3; LR-, 0.21), lateral indentation depth ≥ 7 mm (sensitivity, 95%; specificity, 77.5%; LR+, 4.2; LR-, 0.06) and T-angle $\leq 40^\circ$ (sensitivity, 80%; specificity, 87.5%; LR+, 6.4; LR-, 0.23). Most of the experts diagnosed the uterus as being T-shaped in 0% (0/56) of cases when none of these three criteria was met, in 10% (2/20) of cases when only one criterion was met, in 50% (5/10) of cases when two of the three criteria were met, and in 93% (13/14) of cases when all three criteria were met.

Conclusions The diagnosis of T-shaped uterus is not easy; the agreement among experts was only moderate and the judgement of individual experts was commonly insufficient for accurate diagnosis. The three sonographic measurements with cut-offs that we identified (lateral internal indentation depth ≥ 7 mm, lateral indentation angle $\leq 130^\circ$ and T-angle $\leq 40^\circ$) had good diagnostic test accuracy and fair-to-moderate reliability and, when applied in combination, they provided high post-test probability for T-shaped uterus. In the absence of other anomalies, we suggest considering a uterus to be normal when none or only one criterion is met, borderline

when two criteria are met, and T-shaped when all three criteria are met. These three CUME criteria for defining T-shaped uterus may aid in determination of its prevalence, clinical implications and best management and in the assessment of post-surgical morphologic outcome. The CUME definition of T-shaped uterus may help in the development of interventional randomized controlled trials and observational studies and in the diagnosis of uterine morphology in everyday practice, and could be adopted by guidelines on uterine anomalies to enrich their classification systems. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

In the mid-20th century, there were considered to be three basic, normal morphological variants of the uterine cavity: (i) almost triangular in shape; (ii) with small lateral indentations; and (iii) with greater fundal and lateral indentations (Figure 1)^{1,2}. T-shaped uterus was first described, based on hysterosalpingography findings, as a diethylstilbestrol (DES)-related congenital uterine anomaly, with the uterine cavity shape resembling the letter 'T'³⁻⁷. Considering the DES-related etiology and morphology, T-shaped uterus was grouped by Buttram and Gibbons⁶ and the American Fertility Society (AFS) classification⁸ into a separate class of anomalies, with no strict definition or morphometric criteria. However, of the 1–1.5 million women exposed to DES *in utero*, before its withdrawal from use during pregnancy in 1971, there remain none of reproductive age^{9,10}, and yet T-shaped uterus continues to be identified in this group of women, albeit rarely, in this post-DES era^{7,11}. T-shaped uterus may be of primary origin¹² or secondary to intrauterine adhesion syndrome⁷, tuberculosis¹³ or adenomyosis¹⁴. It has been suggested that it may be related to reproductive failure, such as infertility^{7,12,15-18} and recurrent miscarriage^{7,12,16-18}, but the clinical relevance of the non-DES-related T-shaped uterus is far from clear and this is not helped by the lack of an objective definition and consensus regarding its diagnosis. However, the quality of evidence is not good.

In 2013, the European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy (ESHRE-ESGE) published a guideline in which T-shaped uterus was defined subjectively as a narrow uterine cavity due to thickened lateral walls¹⁹. It did not specify objective criteria with which to diagnose T-shaped uterus or explain how the uterine measurements should be performed. Among the various modifications of the AFS system, supplemented by morphometric criteria, that of Salim²⁰ did not include T-shaped uterus as an anomaly, that of Ludwin¹¹ did not provide measurable criteria for T-shaped uterus, and the recent official definitions published by the American Society for Reproductive Medicine (ASRM)²¹ are for only normal/arcuate, septate and bicornuate uterus. Until now, no objective and measurable criteria have been described for identifying T-shaped uterus, and this is a considerable

Figure 1 Three basic types of normal uterine cavity based on hysterosalpingography, according to Schultze and Erbsloh¹: (a) triangular cavity; (b) cavity with small fundal and lateral indentations; and (c) cavity with larger fundal and lateral indentations.

barrier to amassing evidence on its prevalence, its clinical implications and optimal management of this morphology.

Recently, the Congenital Uterine Malformation by Experts (CUME) initiative was developed to establish measurable criteria and definitions for normal and abnormal uterine morphology, build common language and unify the classification systems based on reliability/agreement and accuracy testing²². This methodology is based on the assumption that the option selected most often by several independent experts, blinded to each others' opinions, regarding uterine images, would be the best available reference standard with which to estimate diagnostic test accuracy and identify the best cut-off values for measurements.

The present study aimed to identify uterine measurements that are sufficiently reliable and accurate to distinguish between T-shaped and normal/arcuate uterus, and define T-shaped uterus, using CUME methodology for the reference standard.

METHODS

Study design

This was a prospectively planned multirater reliability/agreement and diagnostic accuracy study, performed between November 2017 and December 2018. The Guidelines for Reporting Reliability and Agreement Studies (GRRAS)²³ and the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement²⁴ were used in the design and reporting of the study. The standardized design and principles of methodology (the CUME methodology) were similar to those used in our recent study to develop a definition distinguishing between normal/arcuate and septate uterus²². The target reference standard used in the CUME methodology is multiexpert reference standard, and three-dimensional (3D) ultrasound is used as a reference diagnostic tool. The target population is women of reproductive age, with specific uterine appearance, which may be interpreted as T-shaped or normal/arcuate depending on appearance of lateral indentations. This study was part of a large prospective observational project on screening, diagnosis and classification of congenital uterovaginal malformations by ultrasound. The project and this study were approved

by the local ethics committee (KBET/236/B/2013) and written informed consent was obtained from all patients.

We planned to include 3D datasets from 100 different uteri with lateral internal indentations and with fundal internal indentation < 10 mm, identified from all datasets preacquired by an experienced observer from consecutive women between 2014 and 2016. Two independent observers prepared from the 3D datasets two-dimensional (2D) images in the coronal view for all uteri, and 15 invited experts provided independently their subjective assessment of the images. Two raters, who were at level three in terms of experience according to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB, www.efsumb.org), with at least 15 years of experience in 3D ultrasound examination, obtained independently specific target measurements of each uterus using the same unprocessed 3D datasets. The field of expertise, number of years of experience and country of residence of the included experts and observers are presented in Table S1.

Main and secondary outcome measures

Our main outcomes were the CUME process of establishing the reference for diagnosis and classification of T-shaped uterus and the level of agreement among experts in the recognition of T-shaped uterus using subjective judgment based on review of coronal images from 3D ultrasound volumes. Secondary outcomes were: (i) the interobserver reliability/agreement for measurements potentially useful as objective diagnostic criteria for T-shaped uterus and to distinguish T-shaped uterus from normal/arcuate uterus; (ii) the diagnostic test accuracy and the best cut-off values for these measurements, using the CUME reference standard (multiexpert opinion); (iii) a definition of T-shaped uterus, using the most accurate and reliable objective measurable criteria with reasonable post-test probability of this morphology, suitable for use in trials, observations and clinical practice.

Setting and patients

The study included 3D ultrasound datasets of uteri from women of reproductive age (18–45 years), who were recruited for detailed evaluation at a single recruitment center, a private clinic (Ludwin and Ludwin Gynecology,

Krakow, Poland) specializing in the management of congenital uterine anomalies. Excluded from the main project were women with unexpected pregnancy detected during the evaluation, menopause, malignancy, benign lesions distorting the uterine cavity shape and/or uterine wall, and those with previous uterine surgery. Obvious uterine morphologies that were not considered as T-shaped uteri (namely, normal/arcuate uterus without lateral indentation, uterine agenesis and unicornuate, bicornuate, didelphic and septate uteri) were ineligible for this study. Asymmetrical uteri with a lateral indentation on one side were not excluded.

For the main project, all patient data and 3D ultrasound datasets were collected prospectively and aggregated in a large database at Jagiellonian University, Department of Gynecology and Oncology, Krakow, Poland. However, for the purposes of the current study we retrieved using online software (Google forms and Dropbox) only stored unprocessed 3D ultrasound volumes; the demographic data, previous measurements and previous real-time and offline diagnoses were not used and did not influence the study results.

Ultrasound examination

The ultrasound imaging technique used has been described previously^{11,22}. Uteri were evaluated by 2D and 3D transvaginal ultrasound (or transrectal in case of intact hymen). Voluson E8 and Expert BT13 (GE Healthcare, Zipf, Austria) ultrasound systems, equipped with volumetric intravaginal probes (GE RIC, 5–9 MHz), were used for acquisition of 3D datasets in a standardized manner (sagittal view of uterus; maximum sweep angle 120° and maximum quality; approximate angle between ultrasound beam and uterine axis = 90°; 3D volume acquisition while patient breath-held and refrained from movement). Two different 3D datasets of each uterus were obtained, recorded and stored for all women, after confirmation that the entire uterus had been captured in the 3D volume. If necessary, the acquisition was repeated in the transverse plane, which is more appropriate than acquisition in the sagittal plane for uteri with larger transverse diameter, although in these acquisitions the entire uterus with cervix may be only partially visible in the coronal view. Women with regular menstrual cycles were examined between days 17 and 25 of the cycle, since the secretory phase facilitates visualization of the endometrial cavity. Women with irregular cycles or amenorrhea and those using hormonal contraception were examined independently of the stage of the menstrual cycle, but not during menstruation. All ultrasound examinations were performed in real time by one of two experienced sonologists (I.L., A.L.; experience level three, according to EFSUMB, and at least 15 years of experience with 3D-US).

Sample size

The sample sizes for subjects ($n=100$), raters for subjective judgment ($n=15$), observers for preparing

the images to be sent to the experts ($n=2$) and raters for performing the measurements ($n=2$) are standardized for our CUME exploratory studies for specific definitions, and are based on the available guidelines for reliability/agreement studies^{25,26}. In fact, it has been argued in the field of reliability studies that the increase in precision of reliability coefficients achieved by using sample sizes of more than 50 subjects and more than three raters is rarely worth the additional effort required²⁷. However, we chose arbitrarily to increase our target sample size to 100 subjects in order to achieve an interval of confidence of 95% for the concordance correlation coefficient (CCC) of 0.2, considering the expected CCC of at least 0.80 by two raters. Also, as in our previous study²², we similarly selected arbitrarily an increased sample size of expert raters, feeling that 15 expert raters (five raters in each of three fields; specifically, clinicians specializing in reproductive medicine and/or congenital uterine anomalies, surgeons, and sonologists) would provide more generalizable results than would be possible with participation of only three experts.

Subject selection and preparation of images

Subject selection for the current study was based on consecutive inclusion of 3D datasets of uteri from women with specific uterine features (presence of uterine cavity lateral indentations). 3D datasets of consecutive women included in the main project were specifically re-assessed for this study by an experienced sonologist (I.L.) until 100 uteri fitting our eligibility criteria had been identified. The presence of lateral indentation was judged subjectively. When present, fundal indentations were measured, to confirm that they were smaller than 10 mm.

A single 3D volume of the uterus of each woman was anonymized, numbered, stored and sent to two observers from another institution (M.A.C.N., W.C., both with 3 years of experience in 3D-ultrasound imaging), who prepared for assessment by the invited experts images of the coronal view, using two different ultrasound techniques. One combined OmniView with volume contrast imaging (VCI); Omniview provides a rendered view of the coronal plane by curved rendered mode, which allows identification of the internal os in the coronal plane of the uterus, and VCI is a tool that enhances the contrast between tissues and organs²⁸. The other, HDlive, also allows use of a curved rendered mode and enhances the depth of perception, generating a realistic appearance²⁹. These imaging modalities were chosen because they were preferred according to independent multiexpert opinion in the first CUME study²². Each of the two observers prepared half of the images and all were then reviewed by two more experienced observers (A.L. and W.P.M.), who confirmed that the correct coronal view of each uterus had been obtained, with both uterine cavity horns, cervical canal and internal cervical os visible. If necessary, the observer was asked to correct the coronal plane and prepare a new image. The pair of images for each uterus were then combined into a single image set (presented

Figure 2 Example of image pairs of two uteri, displayed using two 3D ultrasound modalities: HDlive (a,c) and Omniview with volume contrast imaging (b,d). One hundred such pairs of images were sent to 15 experts for subjective assessment regarding whether uterus was T-shaped, and decision made by the majority (i.e. at least eight of the 15 experts) was used as CUME reference standard. (a,b) Example of uterus which the majority (14/15) decided was not T-shaped. (c,d) Example of uterus which all experts (15/15) judged to be T-shaped.

side-by-side; Figure 2) and all 100 image pairs were sent to each of the 15 experts for subjective judgment regarding whether the uterus was T-shaped. Subjective judgment was used because, at this level of expertise (especially clinicians and surgeons), it is common practice that final diagnosis is made in this way, i.e. subjectively based on imaging results. Ultrasound measurements were also performed offline by two expert raters (A.L and W.P.M.) independently, using the unprocessed 3D volumes.

Expert selection

The principles and eligibility criteria for recruitment of experts were the same as those described previously for building the CUME group, based on reliable information about expertise²². We invited to join the CUME group: (i) editors-in-chief/deputy editors/members of editorial boards of journals with the highest impact in the fields of gynecology and reproductive medicine, imaging and/or gynecological surgery; (ii) presidents or members of

executive committees of nine targeted societies in the field (Table S1); and (iii) experts globally well-known in these fields due to their publications on uterine anomalies. All invited experts had at least 50 publications in the field of obstetrics, gynecology, gynecological surgery and/or imaging and all were required to give their consent to participate. Considered as ineligible were experts involved in previous consensus on the measurable criteria for congenital uterine malformations, those with known potential personal or financial conflict of interest regarding promotion of specific criteria, societies or surgical procedures (surgery of T-shaped uterus) and close friends or coworkers from the same institutions. Hence, we used the same initial list of 15 experts and supplementary list of six experts (two per field) that were used in the first CUME study²². If someone from the initial list did not agree to participate or had not responded within 7 days, we then invited consecutively from the supplementary list another expert from the same field. To avoid bias, the experts were blinded to the opinions of each other.

Rating process

An online questionnaire was created for this study and the link (<https://goo.gl/forms/s947iFtit5T7rwBf2>) was sent to the members of the expert panel (CUME group). This presented the experts with a dichotomous question for each image pair: T-shaped *vs* not T-shaped.

Clinical definitions for experts

We did not consider it appropriate to define and recognize T-shaped uterus according to clinical definitions regarding additional morphological features, benchmarks or potential reproductive outcomes of this morphology because there are no objective criteria with which to identify T-shaped uterus and there is no evidence regarding whether T-shaped uterus (that is not DES-related) is associated with worse reproductive outcome. We also avoided any suggestions that T-shaped uterus is a congenital uterine malformation because there is no evidence that this morphology is a result of embryological disorders. The experts were simply asked to identify subjectively uterine cavities as (i) T-shaped or (ii) not T-shaped. The experts had no access to any measurement or clinical information, with the exception that they knew that none of the included women had been exposed to DES.

Ultrasound measurements and their selection

Two experts (A.L., W.P.M.), who were blinded to the opinion of the other experts, proposed independently potentially useful measurements for differentiation of T-shaped uterus from normal/arcuate uterus. Through discussion, they established a standardized set of 15 measurements (11 types of measurement, with four being pairs of symmetrical measurements performed on both left and right sides) and their methodology. Any measurement without a direct association with the uterine cavity was not considered; for example, uterine-wall thickness, because the uterine cavity shape and degree of deformity are commonly independent of this. We tested each of the symmetrical measurements separately and also calculated their average. Additionally, ratios of some of the measurements were selected for calculation by consensus.

The proposed measurements, illustrated in Figure 3 and detailed in Table 1, were: fundal internal indentation depth^{22,30}; lateral internal indentation depth (on left and right sides); circle area of the uterine cavity; uterine cavity area, traced manually; uterine cavity circumference; uterine cavity length; uterine cavity width; fundal indentation angle; lateral indentation angles (right and left); cornual angles (right and left); and T-angle. We determined the position of the internal os by subjective impression based on three criteria: the region of echogenicity transition (myometrium is brighter and cervix is darker), the position of uterine vessels, and the narrowest point of the 'hourglass sign' formed between the uterine and cervical cavities.

The two observers performing the measurements (A.L. and W.P.M.) did so by manipulating independently the same initial dataset of each uterus, to obtain the midcoronal plane of the uterus, using Omniview with VCI mode. Omniview with VCI was selected for the measurements because it is easier to manipulate compared with HDlive and it facilitates identification of the internal os.

Bayes' theorem and definition of T-shaped uterus

Assessment of reliability/agreement and accuracy to identify the best of the 15 measurements was the first step in the selection of criteria and development of a definition for T-shaped uterus. Bayes' theorem adopted by Fagan³¹ was used to quantify the post-test probability of T-shaped uterus and to establish a definition considering the highest post-test probability of women in the target population having T-shaped uterus. This approach is standard in evidence-based medicine³² and clinically applied epidemiology for interpretation of diagnostic accuracy studies³³.

Statistical analysis

Analyses were conducted using GraphPad Prism version 6 (GraphPad Software Inc., San Diego, CA, USA), IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) and Stata version 13.0 (StataCorp LP, College Station, TX, USA). Agreement between all experts, and agreement between experts with respect to area of expertise (clinicians, surgeons and sonologists) was assessed using the kappa index (Fleiss kappa for multiple raters) and proportion of agreement (percent agreement)³⁴. The margins of variability/error between the two experts who performed the measurements were estimated by limits of agreement (LoA). Interobserver reliability and agreement of the uterine measurements were expressed by the CCC and LoA and the coefficient of repeatability (CoR). These statistical indices and coefficients were interpreted with regard to reporting strength of agreement/reproducibility as follows³⁵: poor: kappa < 0.2, ICC/CCC < 0.7, CoR (relative differences) > 50%; fair: kappa 0.2–0.4, ICC/CCC 0.7–0.9, CoR (relative differences) 20–50%; moderate: kappa 0.41–0.60, ICC/CCC 0.90–0.95, CoR (relative differences) 10 to < 20%; good: kappa 0.61–0.80, ICC/CCC 0.95–0.99; CoR (relative differences) 5 to < 10%; very good: kappa 0.81–1.00, ICC/CCC > 0.99; CoR (relative differences) < 5%.

The area under the receiver-operating-characteristics curve (AUC) was used to estimate diagnostic test accuracy, and Youden's index was used to find the best cut-off value, according to the CUME reference standard. Sensitivity, specificity and negative and positive likelihood ratios (LR– and LR+) were calculated. A Fagan nomogram generated online by Schwartz's calculator (<http://araw.mede.uic.edu/cgi-bin/testcalc.pl>) was used to estimate by how much the most accurate criteria and their combination would change the probability of a

Figure 3 Demonstration of 15 proposed measurements for recognition of T-shaped uterus: (a) fundal internal indentation depth; (b) right lateral internal indentation depth; (c) left lateral internal indentation depth; (d) circle area of uterine cavity (ellipse function); (e) uterine cavity area (manual trace); (f) uterine cavity circumference; (g) uterine cavity length from intercornual line to internal os; (h) uterine cavity width (intercornual); (i) fundal angle and right and left lateral indentation angles; (j) right and left cornual angles; (k) right T-angle; (l) left T-angle. Symmetrical measurements from left and right sides were used to calculate average value for these measurements. Selected measurements were used for creation of indices: uterine cavity area/uterine cavity circle area, uterine cavity area/uterine cavity circumference and uterine cavity area/uterine cavity circumference².

uterus being T-shaped (posterior probability) in the target population³¹. Pretest probability was based on the prevalence of T-shaped uterus according to the diagnosis made most often by experts in the target population (suspicion of T-shaped uterus). Agreement, diagnostic accuracy of each of the invited experts (subjective judgment of single experts), diagnoses based on the most accurate measurements and combinations of these measurements in comparison with the CUME reference standard were expressed by the kappa statistic, and their accuracy was compared using the McNemar test. We assessed the correlation (Spearman's) of each parameter with the sum of votes from the invited experts. Statistical significance was defined by $P \leq 0.05$.

RESULTS

3D datasets of 2179 uteri of consecutive women were assessed as potentially eligible in order to select for inclusion in the study a sample of 100 3D datasets of uteri with lateral internal indentation.

Diagnosis of T-shaped uterus

According to CUME, using as reference standard the decision made most often by the experts (i.e. by eight or more of the 15), there were 20 T-shaped and 80 normal/arcuate uteri. The median number of diagnoses of T-shape per expert was 19, and the minimum and maximum diagnoses of T-shape per expert were 5 and 35, respectively (Table 2).

Agreement between experts (subjective evaluation)

Of the 1500 decisions overall (15 experts $\times$ 100 datasets), there were 305 (20%) of T-shaped uterus, with a moderate level of agreement between experts (kappa = 0.43) and an observed agreement of 82% (Table 3). There were differences in level of agreement as expressed by kappa among the different groups of experts: sonologists and clinicians had a moderate level of agreement (kappa = 0.45 and 0.48, respectively), while surgeons achieved a fair level (kappa = 0.31). Percent agreement was close to

Table 1 Description of 15 proposed ultrasound measurements for differentiation of T-shaped uterus from normal/arcuate uterus

Parameter	Unit	Description
Fundal internal indentation depth	mm	Distance between intercornual line (line connecting highest points of endometrial cavity on each side of uterus) and lowest point/nadir of fundal internal indentation ^{22,30}
Lateral internal indentation depth		
Right	mm	Distance between line connecting internal os to most lateral point of uterine cavity and line crossing apex of lateral indentation, right side
Left	mm	Distance between line connecting internal os to most lateral point of uterine cavity and line crossing apex of lateral indentation, left side
Circle area of uterine cavity	cm ²	Area of circle touching three points (two most lateral points of uterine cavity and internal os)
Uterine cavity area	cm ²	Area of uterine cavity (traced manually), including all external limits of endometrial cavity, and inferior limit being internal os
Uterine cavity circumference	cm	Circumference of uterine cavity (traced manually)
Uterine cavity length	mm	Distance between intercornual line and internal os
Uterine cavity width	mm	Distance between two most lateral points of uterine cavity
Fundal indentation angle	degrees	Based on three points: apex/lowest point of fundal internal indentation and two points on myometrial/endometrial interface, 5 mm distant from first point, one to each side of it
Lateral indentation angle		
Right	degrees	Based on three points: apex of right lateral indentation and two points on myometrial/endometrial interface, 5 mm distant from first point, one to each side of it
Left	degrees	Based on three points: apex of left lateral indentation and two points on myometrial/endometrial interface, 5 mm distant from first point, one to each side of it
Cornual angle		
Right	degrees	Based on three points: most lateral point of uterine cavity on right side, and two points on myometrial/endometrial interface, 5 mm distant from first point, one to each side of it
Left	degrees	Based on three points: most lateral point of uterine cavity on left side, and two points on myometrial/endometrial interface, 5 mm distant from first point, one to each side of it
T-angle		
Right	degrees	Based on three points (most lateral point of uterine cavity on right side, contralateral most lateral point of uterine cavity and apex of ipsilateral lateral indentation)
Left	degrees	Based on three points (most lateral point of uterine cavity on left side, contralateral most lateral point of uterine cavity and apex of ipsilateral lateral indentation)
Uterine cavity area/uterine cavity circle area	None	Uterine cavity area (traced manually) divided by area of circle touching three points (most lateral points of uterine cavity and internal os)
Uterine cavity area/uterine cavity circumference	None	Uterine cavity area (traced manually) divided by uterine cavity circumference (manual drawing)
Uterine cavity area/uterine cavity circumference ²	None	Uterine cavity area (traced manually) divided by (circumference of uterine cavity) ²

Table 2 Diagnoses of T-shaped uterus by subjective judgment of 15 experts, overall and according to their field of expertise

Expert	Number of diagnoses of T-shape					Total
	Median	p25–p75	Range	Mean	SD	
Clinicians (<i>n</i> = 5)	33	19.5–34.5	17–35	28.2	8.2	141
Sonologists (<i>n</i> = 5)	17	6.5–24	6–29	15.6	9.5	78
Surgeons (<i>n</i> = 5)	16	9.5–25.5	5–27	17.2	8.7	86
All (<i>n</i> = 15)	19	14–29	5–35	20.3	10.0	305

Number of uteri = 100. p25–p75, lower–upper quartile.

Table 3 Agreement between experts in recognizing T-shaped uterus using subjective judgment of mid-coronal view of uterus from three-dimensional ultrasound

Expert	T-shape selected (n/N (%))	Kappa (95% CI)	Percent agreement (95% CI); n/N*
Clinicians (<i>n</i> = 5)	141/500 (28)	0.48 (0.41–0.55)	79 (76–81); 790/1000
Sonologists (<i>n</i> = 5)	78/500 (16)	0.45 (0.41–0.49)	86 (83–88); 856/1000
Surgeons (<i>n</i> = 5)	86/500 (17)	0.31 (0.23–0.39)	80 (78–83); 804/1000
Overall (<i>n</i> = 15)	305/1500 (20)	0.43 (0.39–0.47)	82 (81–82); 8566/10 500

Number of uteri = 100. *Considering each subgroup of experts (*n* = 5), there are 10 pairwise comparisons for each uterus (Rater 1 vs Rater 2, Rater 1 vs Rater 3, Rater 1 vs Rater 4, ...), resulting in a total of 1000 comparisons when assessing 100 subjects; considering all 15 experts, there are 105 pairwise comparisons for each uterus, resulting in a total of 10 500 comparisons.

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80%, with the highest percent agreement being among expert sonologists (86%), followed by surgeons (80%) and clinicians (79%). Clinicians diagnosed T-shaped uterus more often (28%) than did surgeons (17%) and sonologists (16%).

Interobserver reliability/agreement of ultrasound measurements

The results of all measurements performed by the two observers, and the interobserver reliability/agreement of these measurements, are shown in Tables S2 and S3, respectively. Three measurements were identified as having good accuracy for the diagnosis of T-shaped uterus: average lateral internal indentation depth, average lateral indentation angle and T-angle.

Their reliability was as follows: CCC = 0.82, 0.62 and 0.87, respectively (Table 4). Relative and absolute differences between the measurements of the two observers for these three measurements are shown in Table 4 and Figure 4.

Diagnostic test accuracy of measurements

The diagnostic test accuracy of all measurements, using experts (CUME) as reference standard, is shown in Table S4. The lateral indentation angle (AUC = 0.95), lateral indentation depth (AUC = 0.92) and T-angle (AUC = 0.87) had good diagnostic test accuracy compared with subjective impression by experts (Table 5). The best cut-off values for these measurements were: lateral indentation angle $\leq 130^\circ$ (sensitivity = 80%,

Table 4 Interobserver reliability/agreement of three most accurate measurements selected from 15 potentially useful measurements to establish objective diagnostic criteria for T-shaped uterus

Measurement	Absolute difference		Relative difference		CCC (95% CI)
	LoA	CoR	LoA (%)	CoR (%)	
Lateral indentation depth	-1.0 mm to 2.2 mm	1.6 mm	-17 to 36	26	0.82 (0.75–0.87)
Lateral indentation angle	-19° to 19°	19°	-14 to 14	14	0.62 (0.48–0.73)
T-angle	-9° to 7°	8°	-20 to 15	18	0.87 (0.82–0.91)

Number of uteri = 100. CCC, concordance correlation coefficient; CoR, coefficient of repeatability; LoA, limits of agreement.

Figure 4 Bland-Altman plots for absolute (a–c) and relative (d–f) differences observed between uterine measurements of two expert observers: (a,d) lateral internal indentation depth; (b,e) lateral indentation angle; and (c,f) T-angle. Measurements are averages of left and right sides.

specificity = 96%, LR⁻ = 0.21, LR⁺ = 21.3), lateral indentation depth ≥ 7 mm (sensitivity = 95%, specificity = 78%, LR⁻ = 0.06, LR⁺ = 4.2) and T-angle $\leq 40^\circ$ (sensitivity = 80%, specificity = 88%, LR⁻ = 0.23, LR⁺ = 6.4). Table S5 presents these best cut-offs for the selected measurements and their agreement with multi-expert opinion.

The criteria, their frequency and diagnosis

Among the 100 uteri assessed, the numbers meeting none, some or all of the three criteria identified as most accurate for identifying T-shape (lateral internal indentation depth, lateral indentation angle and T-angle), along with the corresponding numbers of those considered to be T-shaped or normal/arcuate, according to the diagnosis made most often by experts (CUME), were as follows:

- Met no criteria: $n = 56$; all of these were considered normal/arcuate uterus;
- Met only one criterion: $n = 20$, of which: 2 considered T-shaped; 18 considered normal/arcuate uterus;
- Met any two criteria: $n = 10$, of which: 5 considered T-shaped; 5 considered normal/arcuate uterus;
- Met all three criteria: $n = 14$, of which: 13 considered T-shaped; 1 considered normal/arcuate uterus.

Post-test probability of T-shaped uterus by three most accurate measurements and their combination

In Figure 5, by means of the Fagan nomogram, we present the estimated post-test probability of T-shaped uterus for the target population, based on the known 20% pretest probability of T-shaped uterus (20/100 diagnoses of T-shaped uterus according to the diagnosis made most often by CUME experts) and the LR⁺ (for presence of the

Table 5 Diagnostic test accuracy of three best measurements selected from 15 potentially useful measurements to establish objective diagnostic criteria for T-shaped uterus

Measurement	AUC (95% CI)	Spearman's ρ^*	Cut-off	Sensitivity (% (95% CI); n/N)	Specificity (% (95% CI); n/N)	Youden's index (J)
Lateral indentation depth	0.92 (0.87–0.98)	0.66	≥ 7 mm	95 (75–100); 19/20	77.5 (67–86); 62/80	0.73
Lateral indentation angle	0.95 (0.90–0.99)	–0.73	$\leq 130^\circ$	80 (56–94); 16/20	96 (89–99); 77/80	0.76
T-angle	0.87 (0.78–0.95)	–0.62	$\leq 40^\circ$	80 (56–94); 16/20	87.5 (78–94); 70/80	0.68

We considered as reference standard the diagnosis made most often among 15 experts. *Correlation with sum of diagnoses.

Figure 5 Fagan nomograms to determine probability of having T-shaped uterus based on optimal criteria identified in this study and on diagnosis made most often by experts as reference standard²²: lateral indentation angle $\leq 130^\circ$ (a), lateral indentation depth ≥ 7 mm (b) and T-angle $\leq 40^\circ$ (c) as single diagnostic criteria, and CUME definition of T-shaped uterus (presence of all three criteria) (d). Straight lines run from patient's pretest probability of T-shaped uterus (Prior prob.), in cases suspected of having T-shaped uterus due to presence of lateral cavity indentation (i.e. 20%), to their post-test probability of disease (Post. prob.), representing positive (---) and negative (—) likelihood ratios (LR) for presence and absence, respectively, of each criterion individually (a–c) and in combination (all three criteria present or absent) (d). Post-test probability of uterus being T-shaped increased 2–4-fold in presence of lateral indentation angle $\leq 130^\circ$ (c. 84%) or depth ≥ 7 mm (c. 51%) or T-angle $\leq 40^\circ$ (c. 62%) and was highest (c. 93%) in presence of all three, while it was very low (1–5%) or low (8%) in absence of one of these three or all three (CUME definition), respectively.

criterion) or LR– (for absence of the criterion) values, for each criterion individually (diagnosis of T-shaped uterus in presence of each) and for their combination (diagnosis of T-shaped uterus in presence of all three criteria). The post-test probabilities of a uterus being T-shaped in the presence of lateral indentation angle $\leq 130^\circ$, lateral indentation depth ≥ 7 mm, and T-angle $\leq 40^\circ$ were 84%, 51% and 62%, respectively, and in the absence of these criteria they were 5%, 1% and 5%, respectively. The post-test probability of a uterus being T-shaped in the presence of all three criteria was 93% and in the absence of this combination of all three (negative test results) it was 8%.

Individual experts' opinions vs measurements vs CUME reference

The diagnostic accuracy measures and agreement expressed by kappa of individual experts, according to individual criteria and combinations of the three criteria relative to the CUME reference, i.e. the decision made most often by the experts, is shown in Table 6. The presence of at least two criteria or all three criteria performed better than did most of the experts individually (13 and 11 experts, respectively) compared with the CUME reference (kappa = 0.77 and 0.72). The proportion, among the 100 datasets, of diagnoses of T-shaped uterus by several individual experts was significantly different from the proportion determined using the CUME reference (McNemar test, $P < 0.05$), while combination of any two or of all three measurements were not significantly different (McNemar test, $P > 0.05$).

DISCUSSION

This study illustrates the challenging nature of the diagnosis of T-shaped uterus. The level of agreement between experts asked to distinguish subjectively between T-shaped and not T-shaped uterus based on assessment of a coronal view of the uterus from a 3D ultrasound dataset was moderate (kappa = 0.43) and the agreement was 82%. To our knowledge, this is the first study to define objectively T-shaped uterus. Also, our findings are relevant to establishment of a definition for this morphological variant of normal uterus, including both the uterine cavity lateral indentation criteria addressed herein and previously published fundal internal indentation criteria (depth < 10 mm)²².

We identified three sonographic measurements that had good diagnostic accuracy and fair to moderate interobserver reproducibility: lateral indentation angle (AUC = 0.95, CCC = 0.62, CoR = 14%), lateral internal indentation depth (AUC = 0.92, CCC = 0.82, CoR = 26%) and T-angle (AUC = 0.87, CCC = 0.87, CoR = 18%). Based on these results, we suggest, for the purpose of research and description of uterine morphology in clinical practice, definitions for normal/arcuate uterus, borderline T-shaped uterus and T-shaped uterus (Table 7) and we establish the CUME definition of T-shaped uterus as follows: lateral indentation angle $\leq 130^\circ$; lateral internal indentation depth ≥ 7 mm and T-angle $\leq 40^\circ$ (Figures 6, 7 and S1).

With the suggested diagnosis based on three ultrasound measurements, it was possible to achieve better agreement with the diagnosis selected most often by the group of 15

Table 6 Diagnostic accuracy measures and agreement expressed by kappa for diagnoses made by individual experts, or by combinations of three ultrasound measurement criteria, relative to decision made most often among all 15 experts (CUME reference)

	TP (n)	FN (n)	TN (n)	FP (n)	OA (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	LR+	LR–	Kappa (95% CI)	P
Expert 1	20	0	71	9	91	100	89	69	100	8.9	0.00	0.76 (0.61–0.90)	0.004
Expert 2	14	6	75	5	89	70	94	74	93	11.2	0.32	0.65 (0.46–0.84)	1.00
Expert 3	6	14	80	0	86	30	100	100	85	> 100	0.70	0.41 (0.18–0.64)	< 0.001
Expert 4	16	4	79	1	95	80	99	94	95	64.0	0.20	0.83 (0.69–0.98)	0.375
Expert 5	7	13	80	0	87	35	100	100	86	> 100	0.65	0.46 (0.23–0.69)	< 0.001
Expert 6	18	2	65	15	83	90	81	55	97	4.8	0.12	0.57 (0.40–0.75)	0.002
Expert 7	17	3	75	5	92	85	94	77	96	13.6	0.16	0.76 (0.60–0.92)	0.727
Expert 8	14	6	77	3	91	70	96	82	93	18.7	0.31	0.70 (0.52–0.88)	0.508
Expert 9	18	2	64	16	82	90	80	53	97	4.5	0.13	0.55 (0.38–0.73)	0.001
Expert 10	20	0	65	15	65	100	81	57	100	5.3	0.00	0.63 (0.48–0.79)	< 0.001
Expert 11	14	6	70	10	84	70	88	58	92	5.6	0.34	0.54 (0.34–0.73)	0.454
Expert 12	9	11	75	5	84	45	94	64	87	7.2	0.59	0.44 (0.21–0.67)	0.210
Expert 13	13	7	77	3	90	65	96	81	92	17.3	0.36	0.66 (0.47–0.85)	0.344
Expert 14	5	15	80	0	85	25	100	100	84	> 100	0.75	0.35 (0.12–0.58)	< 0.001
Expert 15	20	0	73	7	93	100	91	74	100	11.4	0.00	0.81 (0.67–0.94)	0.016
LI angle	16	4	77	3	93	80	96	84	95	21.3	0.21	0.78 (0.62–0.93)	1.00
LI depth	19	1	62	18	81	95	78	51	98	4.2	0.06	0.55 (0.38–0.72)	< 0.001
T-angle	16	4	70	10	86	80	88	62	95	6.4	0.23	0.61 (0.42–0.79)	0.18
One or more criterion met*	20	0	56	24	76	100	70	45	100	3.3	0.00	0.48 (0.33–0.64)	< 0.001
Two or more criteria met*	18	2	74	6	92	90	93	75	97	12.0	0.11	0.77 (0.61–0.92)	0.289
All three criteria met*	13	7	79	1	92	65	99	93	92	52.0	0.35	0.72 (0.54–0.90)	0.070

Number of uteri = 100. *Criteria: lateral indentation angle $\leq 130^\circ$; lateral indentation depth ≥ 7 mm; T-angle $\leq 40^\circ$. FN, false negative; FP, false positive; LR+, positive likelihood ratio; LR–, negative likelihood ratio; LI, lateral indentation; NPV, negative predictive value; OA, observed agreement; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; TN, true negative; TP, true positive.

Table 7 Criteria and definitions proposed by CUME for classification of uterine morphology as normal/arcuate, borderline T-shaped and T-shaped uterus

Morphology	Number of criteria*
Normal/arcuate uterus	None or only one
Borderline T-shaped uterus	Only two
T-shaped uterus	All three

This classification should be applied only when there is no internal fundal indentation ≥ 10 mm (according to CUME²²) and there are no other subjectively recognized anomalies. *Criteria: lateral indentation angle $\leq 130^\circ$; lateral indentation depth ≥ 7 mm; T-angle $\leq 40^\circ$.

experts (CUME reference) than did most of the experts individually. Reproducibility of these measurements was only fair to moderate³⁵, even though these were well-trained observers. It is, therefore, important to undergo training before employing these measurements. Attempts should be made to develop technical refinements to improve these measurements (for example, by using an average of three measurements or by creation of software for automated measurements).

We may assume, according to Bayes' theorem, that a true-positive diagnosis using specific morphometric criteria reflects with good accuracy the probability of a patient having this morphology. If one of the three

Figure 6 T-shaped uterus as defined by CUME, according to presence of three criteria beyond particular cut-offs: (a) lateral indentation angle $\leq 130^\circ$, (b) lateral indentation depth ≥ 7 mm and (c) T-angle $\leq 40^\circ$. Presence of two of these three criteria is defined as borderline T-shaped uterus, whereas lack or presence of only one of these criteria is defined as normal uterus with respect to lateral uterine morphology. This definition is supported by reliability and diagnostic accuracy testing of measurements, and by post-test probability $> 90\%$ for target population, considering diagnosis made most often by experts as reference (i.e. CUME).

Figure 7 Examples showing performance of proposed three measurements for definition of T-shaped uterus on 3D ultrasound using Omniview with volume contrast imaging: (a) lateral indentation angle (right and left); (b) lateral indentation depth (right and left); and (c) T-angle (right and left).

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ultrasound criteria identified by the CUME process was met, the probability of the woman having a T-shaped uterus was 50–80%, while if none of the three criteria was met, the probability was very low (Figure 5). The post-test probability of T-shaped uterus based on a single criterion identified by CUME should be considered as insufficient for diagnosis. For instance, 50% of women with internal indentation depth ≥ 7 mm and therefore suspected of having a T-shaped uterus will in fact have a T-shaped uterus and 50% will have a normal uterus. If, for example, these women are included in a surgical randomized controlled trial, both women with T-shaped uterus and those with normal uterus would be treated. Any benefit of the intervention for women with a T-shaped uterus may go undetected, and women with a normal uterus may receive iatrogenic treatment. Moreover, in our sample, 2/20 (10%) women, 5/10 (50%) women and 13/14 (93%) women who met one criterion, two criteria and all three criteria, respectively, actually had T-shaped uterus according to CUME. Based on these study results regarding the ultrasound criteria identified by CUME, we suggest in Table 7 definitions for normal/arcuate uterus, borderline T-shaped uterus and T-shaped uterus. Of note, using our suggested definition for T-shaped uterus based on three sonographic measurements, it is possible to achieve better agreement with the CUME reference, based on the decision made most often by 15 experts, than did most of the experts individually (Table 6).

There are some important limitations of this study.

(i) Although this study was able to define objective

measurable criteria to diagnose T-shaped uterus, with moderate agreement according to multiexpert opinion, the clinical relevance of the non-DES-related T-shaped uterus is unknown. (ii) Measurements were performed by highly trained observers, and using a single 3D ultrasound dataset for each uterus; this may not reflect what happens in clinical reality, in which many sources of variability are present, which may have a negative impact on the accuracy and reliability of diagnoses of uterine anomalies. (iii) We used only datasets with lateral indentation detected subjectively, yet detection of all small lateral indentations by measurement may be more accurate and reliable. (iv) We used only datasets with no other subjectively detected anomaly, which means that the CUME criteria were not tested with other defined or undefined minor or major anomalies, or other variants of normal uterus with respect to uterine cavity shape, size and symmetry. (v) Assessment of the uterus and uterine cavity was limited to the mid-coronal plane, which is flat, whereas assessment of 3D spatial morphology and uterine cavity volume, and their quantification, could be important for a modern classification of uterine morphology³⁶. (vi) For the lateral indentation depth, the internal os was used as a reference point, but this may sometimes be difficult to determine. The observed results should not, therefore, be generalized for screening purposes or for assessing other uterine variants, despite our sample representing a wide spectrum of uteri that may be considered as normal/arcuate uteri by the ASRM classification, and normal but misleadingly labeled as septate uteri by the ESHRE/ESGE classification^{11,22,37}.

Figure 8 Examples of uteri indicating for each the diagnosis made most often by experts, and illustrating recognition of normal (a,b) and T-shaped (c,d) uterus, with very good (12–15 of 15 experts made this diagnosis; (a,d)) and good (8–11 of 15 made this diagnosis; (b,c)) agreement, with decreasing numbers of decisions for normal uterus from top to bottom.

The decision to include particular cases might have led to some selection bias.

This study may make an important contribution to the development of a common language for uterine morphology and in the further development of a single, global classification system, with unification of the criteria of various different, more local, classifications, such as those of ESHRE-ESGE and ASRM. Moreover, our results may help in understanding and validating the quality of evidence on T-shaped uterus, and may help to improve the quality of studies and our understanding of this morphology. It may well be that non-DES-related T-shaped uterus is not a congenital anomaly and need not be treated as such. Further efforts should be aimed at determining whether T-shaped uterus is a true uterine anomaly with clinical consequences.

The reliability of all studies regarding prevalence, clinical implications and surgical outcome of T-shaped uterus may be interpreted in the context of this CUME study. So far, the diagnosis has been only subjective. However, our study has shown that the agreement, even among experts, of subjective judgments is not very high (Figure 8). An ideal solution would be to obtain a subjective judgment from several experts, but this is impractical in clinical practice. Our proposed CUME criteria might be used as a surrogate for multiexpert opinion to achieve similar results, with better accuracy and agreement with the reference than is achieved by the subjective judgement of most individual experts.

The definition of T-shaped uterus proposed by ESHRE/ESGE, a 'narrow uterine cavity due to thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 cervix'¹⁹ is arbitrary and was not based on scientific support. By using this definition, it is impossible to differentiate T-shaped uterus from normal uterus and from uterus infantilis, because the reference value of normal uterine-wall thickness and any cut-offs for differentiation of T-shaped uterus from other uterine morphologies were not provided. Interestingly, the ESHRE/ESGE definition has been used retrospectively in some studies^{12,17,38}; however, its application in clinical practice to differentiate between T-shaped uterus and normal uterus is impossible. Before the ESHRE-ESGE classification, T-shaped uterus was recognized according to DES etiology and subjective impression, by the AFS-1988 classification^{8,11}.

Using our results, it should be much easier to study the prevalence of T-shaped uterus and assess its clinical relevance. Until such studies are available, it is suggested not to treat T-shaped uterus as an anomaly, but as a variant of normal uterus, to avoid unnecessary intervention in infertile women or in women with previous miscarriage. Such studies are important in the current era when there is perhaps a tendency towards over-definition of diseases³⁹ and offering 'add-on' intervention to fertility treatment.

In conclusion, the diagnosis of T-shaped uterus is not easy; the agreement among experts was only moderate and the judgment of individual experts was commonly

insufficient for accurate diagnosis. In this study we have identified three ultrasound measurements, with cut-offs, that had good diagnostic test accuracy and fair to moderate reliability (lateral internal indentation depth ≥ 7 mm, lateral indentation angle $\leq 130^\circ$ and T-angle $\leq 40^\circ$) and, when applied in combination, they provided high post-test probability for T-shaped uterus. These three CUME criteria for defining T-shaped uterus may aid in determination of the prevalence, clinical implications, best management of women with this morphology and assessment of post-surgical morphologic outcome with sufficient accuracy and reliability and with a known probability of disease following negative and positive test results. The CUME definition of T-shaped uterus may help in the development of interventional randomized controlled trials and observational studies and in the diagnosis of uterine morphology in everyday practice, and could be adopted by guidelines on uterine anomalies to enrich their classification systems.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Examples of three sonographic measurements to diagnose T-shaped uterus in variants of uterus with lateral indentations: (a) with concomitant small fundal indentation, (b) with cornua of uterine cavity above top of cavity and (c) with cornua of uterine cavity below top of cavity. Measurements illustrated are T-angle (top row), lateral indentation depth (middle row) and lateral indentation angle (bottom row).

Table S1 Details of CUME group for T-shaped uterus reference and observers performing ultrasound measurements to establish objective diagnostic criteria for T-shaped uterus

Table S2 Results of all 15 potentially useful ultrasound measurements performed by two different observers to establish objective diagnostic criteria for T-shaped uterus

Table S3 Interobserver reliability/agreement for all potentially useful ultrasound measurements tested to establish objective diagnostic criteria for T-shaped uterus

Table S4 Diagnostic test accuracy of all potentially useful ultrasound measurements tested to establish objective diagnostic criteria for T-shaped uterus

Table S5 T-shaped uterus according to best cut-off values for selected measurements and their agreement with multiexpert opinion (reference standard)

Figure S1 - Examples of three sonographic measurements to diagnose T-shaped uterus in variants of uterus with lateral indentations: **(a)** with concomitant small fundal indentation, **(b)** with cornues of uterine cavity on top of cavity and **(c)** with cornues of uterine cavity below top of cavity. Measurements illustrated are T-angle (top row), lateral indentation depth (middle row) and lateral indentation angle (bottom row).

Table S1 - Details of CUME group for T-shaped uterus reference and observers performing ultrasound measurements to establish objective diagnostic criteria for T-shaped uterus

Expert	Country of residence	Main affiliation - International Society	Years of experience
Clinicians			
M. Acién	Spain	ESHRE	14 years
A. DeCherney	USA	ASRM	45 years
W. Hurd	USA	ACOG	39 years
A. Pellicer	Spain	ASRM	28 years
F. Petraglia	Italy	ESHRE	34 years
Surgeons			
M. H. Emanuel	The Netherlands	ESGE	31 years
M. P. Diamond	USA	AAGL	32 years
S. Lindheim	USA	ASRM	25 years
E. Saridogan	UK	ESGE	31 years
R-L. de Wilde	Germany	ESGE	36 years
Sonologists			
J. L. Alcazar	Spain	ISUOG	25 years
B. Benacerraf	USA	AIUM	41 years
G. Condous	Australia	ASUM	18 years
S. Guerriero	Italy	ISUOG	31 years
D. Levine	USA	RSNA	22 years
Raters who performed measurements/acquisitions			
A. Ludwin	Poland	ISUOG	19 years
I. Ludwin	Poland	ISUOG	16 years
W. P. Martins	Brazil	ISUOG	16 years

AAGL= American Association of Gynecologic Laparoscopists; **ACOG=** American College of Obstetricians and Gynecologists; **AIUM=** American Institute of Ultrasound in Medicine; **ASRM=** American Society for Reproductive Medicine; **ASUM=** Australasian Society for Ultrasound in Medicine; **ESGE=** European Society for Gynaecological Endoscopy; **ESHRE=** European Society of Human Reproduction and Embryology; **ISUOG=** International Society of Ultrasound in Obstetrics and Gynecology; **RSNA=** Radiological Society of North America.

Table S2 - Results of all 15 potentially useful ultrasound measurements performed by two different observers to establish objective diagnostic criteria for T-shaped uterus

Measurement	Observer 1: A.L.							Observer 2: W.M.P.						
	Median	Q1–Q3	Min-Max	Mean	SD			Median	Q1–Q3	Min-Max	Mean	SD		
Lateral internal indentation depth (mm)	6.5	5.5	8	3.5	11.1	6.7	1.7	5.9	5	7.3	2.9	11.5	6.2	1.6
Circle area of uterine cavity (cm ²)	17.2	14.2	20.6	8.8	33.9	17.3	4.8	17	14.2	19.8	8.6	37.7	17.2	4.6
Uterine cavity area (cm ²)	5.5	4.7	6.5	2.9	10.3	5.6	1.5	5.4	4.5	6.3	2.7	10.5	5.4	1.5
Uterine cavity circumference (cm)	13.3	12.1	14.5	9.4	18.9	13.3	1.8	12.9	12	14	8.9	19.8	13.1	1.8
Uterine cavity length (mm)	37.6	33.1	41.6	26.8	54.3	37.7	5.6	38.1	34.6	42.6	22.8	54	38.6	6
Uterine cavity width (mm)	37.2	33.1	41.5	23.4	60.2	37.6	6.5	36.2	32	40.3	22.7	60.9	36.1	6.2
Fundal internal indentation angle (degrees)	169	156	175	134	214	167.6	16.5	158	151	170	123	213	160.9	16.9
Lateral indentation angle: right (degrees)	137	126	146	93	171	136.1	15.2	141	131	150	97	165	139.5	14
Lateral indentation angle: left (degrees)	142	134	151	89	168	141.4	12.9	140	131	147	105	157	138.1	11.6
Lateral indentation angle: average (degrees)	139	133	147	98	160	138.7	11.6	141	134	146	101	160	138.8	10.6
Cornual angle: right (degrees)	63	52.4	75.8	34.3	114.9	65.4	18.1	53	44	63.7	28.1	96.6	54.1	14.4
Cornual angle: left (degrees)	59.9	48	73.7	31	119.4	61.2	16.9	52.7	43.5	62.2	29.9	89.2	53.8	13.1
Cornual angle: average (degrees)	62.3	50.3	74.9	33.7	98.3	63.3	16	53	45.2	64.1	29.7	92.9	53.9	12.9
T-angle: right (degrees)	45.7	38.5	51.4	19	65.1	45.3	8.4	47.2	39.8	54.1	19.8	66.8	47.4	9.6
T-angle: left (degrees)	45.5	41.7	54.2	24.8	73.2	47.7	9.9	48.3	43.6	55.2	20.8	68.5	48	9.1
T-angle: average (degrees)	46.7	40.9	51.4	22	63.5	46.5	8.3	47.9	42.1	53.3	20.3	63.6	47.7	8.6
Uterine cavity area/uterine cavity circle area	0.32	0.29	0.36	0.23	0.51	0.33	0.05	0.31	0.28	0.36	0.21	0.47	0.32	0.05
Uterine cavity area/uterine cavity circumference	0.42	0.35	0.47	0.28	0.59	0.41	0.07	0.41	0.36	0.45	0.26	0.61	0.41	0.07
Uterine cavity area/uterine cavity circumference ²	0.03	0.03	0.03	0.02	0.05	0.03	0	0.03	0.03	0.04	0.02	0.05	0.03	0

n= 100 uteri; **Q1–Q3**= lower-upper quartile.

Table S3 - Interobserver reliability/agreement for all 15 potentially useful ultrasound measurements tested to establish objective diagnostic criteria for T-shaped uterus

	MD	SD	LoA		CoR	CCC	95% CI	
Fundal internal indentation depth (mm)	-0.13	1.00	-2.09	1.82	1.95	0.91	0.87	0.94
Right lateral internal indentation depth (mm)	0.44	1.43	-2.36	3.25	2.81	0.78	0.69	0.84
Left lateral internal indentation depth (mm)	0.64	1.06	-1.44	2.71	2.08	0.83	0.76	0.88
Circle area of uterine cavity (cm ²)	0.13	2.17	-4.13	4.38	4.25	0.90	0.85	0.93
Uterine cavity area (cm ²)	0.17	0.40	-0.62	0.96	0.79	0.96	0.94	0.97
Uterine cavity circumference (cm)	0.24	0.76	-1.26	1.73	1.50	0.90	0.85	0.93
Uterine cavity length (mm)	-0.88	3.24	-7.23	5.48	6.35	0.84	0.77	0.89
Uterine cavity width (mm)	1.47	2.15	-2.75	5.68	4.22	0.92	0.88	0.94
Fundal indentation angle (degrees)	6.78	12.55	-17.82	31.38	24.60	0.66	0.55	0.75
Right lateral indentation angle (degrees)	-3.43	11.32	-25.62	18.77	22.19	0.68	0.57	0.77
Left lateral indentation angle (degrees)	3.24	13.24	-22.71	29.19	25.95	0.41	0.24	0.55
Right cornual angle (degrees)	11.34	13.84	-15.80	38.47	27.13	0.52	0.39	0.62
Left cornual angle (degrees)	7.40	11.87	-15.86	30.66	23.27	0.62	0.50	0.71
Right T-angle (degrees)	-2.12	5.16	-12.22	7.98	10.10	0.82	0.74	0.87
Left T-angle (degrees)	-0.33	5.59	-11.29	10.64	10.96	0.83	0.75	0.88
Uterine cavity area / uterine cavity circle area	0.010	0.034	-0.056	0.076	0.07	0.77	0.68	0.84
Uterine cavity area / uterine cavity circumference	0.006	0.023	-0.039	0.050	0.045	0.95	0.92	0.96
Uterine cavity area / uterine cavity circumference ^z	<0.001	0.003	-0.006	0.006	0.006	0.84	0.76	0.89
Lateral internal indentation depth average (mm)	0.59	0.82	-1.02	2.20	1.61	0.82	0.75	0.87
Lateral internal indentation angle average (mm)	-0.10	9.72	-19.15	18.95	19.05	0.62	0.48	0.73
Cornual angle average (degrees)	9.37	10.67	-11.55	30.28	20.91	0.60	0.49	0.69
T-angle average (degrees)	-1.23	4.13	-9.33	6.87	8.10	0.87	0.82	0.91

n= 100 uteri, **MD**= mean difference; **LoA**= limits of agreement; **CoR**= Coefficient of Repeatability; **CCC**= Concordance correlation coefficient, **CI**= Confidence interval.

Table S4 - Diagnostic test accuracy of all 15 potentially useful ultrasound measurements tested to establish objective diagnostic criteria for T-shaped uterus

	Area Under the Curve			Correlation with sum of diagnoses
				Spearman correlation
	Area	95% CI		coefficient
Fundal internal indentation depth	0.55	0.41	0.70	-0.01
Right lateral internal indentation depth	0.86	0.78	0.94	0.57
Left lateral internal indentation depth	0.80	0.68	0.92	0.43
Lateral internal indentation depth average	0.92	0.87	0.98	0.66
Circle area of uterine cavity	0.53	0.38	0.67	-0.08
Uterine cavity area	0.56	0.43	0.70	-0.25
Uterine cavity circumference	0.58	0.44	0.72	0.05
Uterine cavity length	0.57	0.41	0.72	-0.14
Uterine cavity width	0.65	0.53	0.78	0.08
Fundal indentation angle	0.60	0.47	0.73	0.09
Right lateral internal indentation angle	0.89	0.81	0.97	-0.64
Left lateral internal indentation angle	0.85	0.75	0.95	-0.55
Lateral internal indentation angle average	0.95	0.90	0.99	-0.73
Right cornual angle	0.60	0.45	0.76	-0.05
Left cornual angle	0.53	0.38	0.69	-0.14
Cornual angle average	0.58	0.42	0.73	-0.09
Right T-angle	0.85	0.76	0.94	-0.65
Left T-angle	0.83	0.73	0.92	-0.49
T-angle average	0.87	0.78	0.95	-0.62
Uterine cavity area/uterine cavity circle area	0.63	0.49	0.77	-0.30
Uterine cavity area/uterine cavity circumference	0.64	0.52	0.77	-0.41
Uterine cavity area/uterine cavity circumference ²	0.71	0.59	0.83	-0.50

n= 100 uteri

Table S5 - Best cut-off values of selected measurements to define T-shaped uterus, and their agreement with expert opinion (reference standard)

	Cut-off	Sens	95%CI	Spec	95%CI	J	OA	TP	TN	FP	FN	kappa	95%CI
LI angle	<131.6	80	56.3-94.3	96.3	89.4-99.2	0.76	93%	16	77	3	4	0.78	0.69-0.85
LI depth	>6.8 mm	95	75.1-99.9	77.5	66.8-86.1	0.73	81%	19	62	18	1	0.55	0.40-0.67
T-angle	≤42	80	56.3-94.3	87.5	78.2-93.8	0.68	86%	16	70	10	4	0.61	0.47-0.72

N= 100 uteri; **LI**= lateral internal indentation; **J**= Youden index; **OA**= observed agreement; **Sens**= sensitivity; **Spec**= specificity; **FP**= false positive; **FN**= false negative; **TP**= true positive; **TN**= true negative; **CI**= Confidence interval.

Artigo 2: Definitions, prevalence, clinical implications and treatment of T-shaped uterus: systematic review

Ultrasound in Obstetrics and Gynecology

Definitions, prevalence, clinical implications and treatment of T-shaped uterus: systematic review

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Title: Definitions, prevalence, clinical implications and treatment of T-shaped uterus: systematic review

Running Title: T-shaped uterus

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Abstract

Objective: This study aims to summarize the current evidence regarding definitions, diagnosis, prevalence, clinical implications and impact of surgical treatment for T-shaped uterus not related to Diethylstilbestrol (DES) exposure in a systematic review and to highlight what needs to be better clarified regarding T-shaped uterus.

Methods: A search on PubMed, Scopus and EMBASE was performed on Mar-2020. The following search terms were used: t-shaped OR t-shape OR infantile OR (lateral indentation) OR (Diethylstilbestrol OR DES) AND (uterus OR uterine OR uteri), AND (anomaly OR anomalies OR malformation OR malformations). Additionally, we hand-searched reference list from included studies for other relevant publications. All studies presenting any data regarding T-shaped uterus not related to DES exposure including at least 10 women were considered eligible. All the studies regarding DES-related T-shaped uterus were excluded because DES is not used since 1971.

Results: The search has found 2,504 records and 20 studies were included in the systematic review. There are only poor-quality studies (observational and quasi-experimental with before-after design). In most of the studies, the diagnosis of T-shaped uterus was based in three-dimensional US (3D-US) (11/16 studies). There is no consensus on definition of T-shaped uterus, but the most cited criteria (4/16 studies) is the criteria from European Society of Human Reproduction and Embryology and the European Society for Gynecological Endoscopy (ESHRE/ESGE) 2013 (narrow uterine cavity

due to thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 cervix), which is subjective. The prevalence of T-shaped uterus varied from 0.2-10% in the included studies. Regarding etiology of T-shaped uterus except for DES, there was mention to adenomyosis (1 study); adhesions (5 studies) and it was cited as primary condition (3 studies). Worse reproductive outcomes were related to T-shaped uterus due to infertility (9 studies), miscarriage (7 studies), preterm delivery (2 studies), ectopic pregnancy (1 study) and repeated implantation failure (7 studies). From the studies that analyzed benefits of surgical treatment by hysteroscopic metroplasty (12 studies), some of them had mentioned some improvement on pregnancy rate (8 studies), live birth rate (7 studies), term delivery rate (4 studies), reduction in miscarriage (5 studies) and ectopic pregnancy (1 study), but the evidence is of very low quality.

Conclusions: Until now, prevalence, clinical relevance, and impact of surgery on reproductive outcomes in women with T-shaped uterus is unknown. There is no clear definition and widely accepted measurable criteria for distinguishing between T-shaped and normal uterus. Some studies correlate T-shaped uterus etiologically with adhesions and adenomyosis. Some studies report improvement on reproductive outcomes after surgery, but the evidence is of very low quality. There are no studies with control group, and it is quite probable that women with normal uterus are being submitted to metroplasty due to still questionable diagnosis of T-shaped uterus.

Key words: Mullerian ducts, Congenital Uterine Anomalies, T-shaped uterus, Dysmorphic uterus

Agreement, lateral indentation, Diethylstilbestrol

For Peer Review

INTRODUCTION

T-shaped uterus is considered a congenital uterine malformation consequent to the failure on later development of the uterus (hypoplastic uterus, T-shaped and diethylbestrol (DES) exposure) ¹. Until de 1980s, T-shaped uterus was commonly related to DES exposure in utero, however women are still presenting T-shaped uterus and its causes remains poorly known ². T-shaped uterus typically exhibits lateral indentations with narrowed uterine cavity ³, in which the shape of the endometrial cavity resemble a "T" ² instead of a triangle.

T-shaped uterus was firstly mentioned by Kauffman in 1977 ⁴ and by Buttran and Gibbons in 1979 ⁵ and later in the classification of the American Fertility Society (AFS) in 1988, as being a type VII or DES-related defect ⁶. In 2013, the European Society of Human Reproduction and Embryology and the European Society for Gynecological Endoscopy (ESHRE-ESGE) ³ proposed a definition for T-shaped uterus as presenting a narrow uterine cavity due to thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 cervix ³.

Because of concerns that T-shaped uterus might be associated with poor reproductive outcomes, hysteroscopic metroplasty has been considered for women with T-shaped uterus. However, there is no robust evidence regarding its effectiveness or safety ².

This study aims to summarize the current evidence regarding T-shaped uterus not related to DES exposure and compile all the information regarding definitions (criteria), diagnosis (diagnostic tools,

accuracy, reliability/agreement), prevalence, clinical implications and effectiveness of interventions for T-shaped uterus in a systematic review and highlight what needs to be better clarified regarding T-shaped uterus.

METHODS

Protocol registration

The protocol of this systematic review has been registered on the International prospective register of systematic reviews (PROSPERO, <http://www.crd.york.ac.uk/prosperto/>). The registration number is CRD42019115131.

Eligibility criteria

All the studies regarding T-shaped uterus not related to DES exposure were included in this systematic review, irrespectively of its design including case series with at least 10 women. We have included studies regardless of their objectives, once we aim to study criteria for definition, diagnostic methods, prevalence, reproductive outcomes and effectiveness of the interventions. We have decided to exclude the studies on DES-related T-shaped uterus because this drug is not used since 1971; if we include those studies, we would actually have a different population than that we are interested, as women currently at reproductive age were not exposed to DES. However, we preferred to include

the term Diethylstilbestrol OR DES in our search, because of the possibility of some authors might continue using the term DES related anomaly to refer to T-shaped uterus.

Search and selection of the studies

We searched PubMed, Scopus and EMBASE using the following search terms: t-shaped OR t-shape OR infantile OR (lateral indentation) OR (Diethylstilbestrol OR DES) AND (uterus OR uterine OR uteri) AND (anomaly OR anomalies OR malformation OR malformations).

The last search was performed in Apr-09-2020. Titles and abstracts were reviewed independently by two authors (WPM and MACN), checking for duplicates and using the pre-established criteria for inclusion (T-shaped uterus not related to DES-exposure). There were no limitations on language, date of publication or status of publication. We hand-searched the reference list of the included studies and related reviews. Some references were manually added according to their relevance if they have not already been identified in the earlier searches.

Three authors (MACN, WPM and AL) retrieved the full-text manuscripts of the references considered to be potentially eligible after screening the abstract. This step was especially difficult once there were very old publications, mainly regarding DES exposure and in other languages but English. One author (AL) also asked help for the librarians of his institution to help on finding the full manuscripts.

Data collection/extraction

Data extraction was performed in a standardized way by two authors (WPM and MACN). Disagreements were solved by consulting a third author (AL). Eligibility was assessed against the inclusion/exclusion criteria, and selected or rejected, as appropriate. The studies were characterized according to its design.

The following data were extracted from the eligible studies: diagnostic criteria and methods of diagnosis mentioned for T-shaped uterus, prevalence, etiology, clinical relevance of the t-shaped uterus on the reproductive outcomes: subfertility, previous miscarriage, recurrent miscarriage, miscarriage per pregnancy, preterm birth, repeated implantation failure, ectopic pregnancy. For the studies that proposed surgical intervention for treating T-shaped uterus, the type of intervention and description of the intervention was extracted together with the reported reproductive outcomes. The primary outcomes were live birth, clinical pregnancy, miscarriage. We have tried to contact the authors of the original studies to obtain additional data whenever necessary.

Assessment of the quality of the studies

For the retrospective observational studies, the Newcastle-Ottawa Quality Assessment Form analyzed the assessment of the risk of bias for Cohort Studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Reliability/agreement studies were judged according to the Quality Appraisal of Diagnostic Reliability (QAREL) ⁷. Diagnostic accuracy studies were judged according to QUADAS-2 ⁸ (<https://www.bristol.ac.uk/populationhealth>

sciences/projects/quadas/quadas-2/). Two researchers (MACN and WPM) have independently assessed the risk of bias, and disagreements were solved by consulting a third author (AL).

Overall quality of the body evidence

The quality of the body of evidence was classified as suggested by GRADE working group (gradeworkinggroup.org/). We assessed the quality of the evidence according to GRADE criteria (risk of bias, consistency of the effect, imprecision, indirectness and publication bias). The quality of the evidence was evaluated according to GRADE criteria independently by two reviewers. Disagreements were solved by discussion.

The quality of the evidence was interpreted as following ⁹: **High quality**: We are very confident that the true effect lies close to that observed on this review. **Moderate quality**: We are moderate confident in the effect estimate. The true effect is likely to be close to the observed on this review, but there is a possibility that it is substantially different. **Low quality**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the observed on this review. **Very low quality**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the observed on this review.

Synthesis of the results

Data was presented in descriptive tables according to the diagnostic criteria, prevalence, clinical relevance and impact of the surgery. As there were no studies considered to be sufficiently similar,

the results of the individual studies couldn't be combined for meta-analysis and they were synthesized in tables.

RESULTS

Study selection and characteristics

The last electronic search was performed on Apr.09.2020, resulting in total of 2,504 records: PubMed (n=505); Scopus (n=750) and Embase (n=1,249). By manual search, we have included 31 additional studies. Of the 2,535 records, 729 were duplicates, remaining 1,806 references. By reading the title/abstract, we could exclude 1,674 references (studies were not regarding T-shaped uterus).

We have evaluated 132 records as potentially eligible; 112 were excluded because:

- T-shaped uterus related to DES = 64 records ¹⁰⁻⁷³
- Not related to T-shaped uterus = 26 records ⁷⁴⁻⁹⁹
- Less than 10 women with T-shaped uterus = 15 records ¹⁰⁰⁻¹¹⁴
- No detailed results for T-shaped uterus = 4 records ¹¹⁵⁻¹¹⁸
- Descriptive reviews = 3 records ¹¹⁹⁻¹²¹

We have included 20 studies in this systematic review ^{2, 122-140} (**Figure 1**).

Diagnosis of T-shaped uterus

Sixteen studies have mentioned the diagnosis of T-shaped uterus. The most cited diagnostic method was three-dimensional ultrasound (3D-US) (11 studies). Others mentioned were magnetic resonance imaging (MRI), hysteroscopy, hysterosalpingography (HSG) and two-dimensional ultrasound (2D-US). Considering that 3D-US and MRI are adequate methods for diagnosing uterine malformations because they allow the visualization of the coronal view of the uterus, eleven studies mentioned at least one adequate method for diagnosing T-shaped uterus (**Table 1**).

From the sixteen studies have mentioned the diagnosis of T-shaped uterus, four studies performed diagnosis of T-shaped uterus in a subjective way ^{126, 129, 130, 138}. Four studies have used the criteria proposed by ESHRE-ESGE ³, in which T-shaped uterus presents a narrow uterine cavity due to thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 uterine cervix ^{122, 141-143}, without specifying definition and cut-off for thickened lateral walls and narrow uterine cavity. Eight studies proposed their own criteria for diagnosing T-shaped uterus ^{2, 123, 124, 127, 135, 139, 144, 145} (**Table 1**). Before proposing their own diagnostic criteria, Neal et al. 2019 ¹²³ and Ludwin et al. 2019 ¹²⁴ have included a step of subjective diagnosis by experts.

One study compared the accuracy of multi-expert subjective opinion to measurements performed by 3D-US ¹²⁴. The definition proposed for T-shaped uterus by the CUME group ¹²⁴ with strict measurable criteria based on diagnosis made most often by independent experts: lateral indentation angle > 130°, lateral indentation depth >7 mm and T-angle ≤ 40° with good diagnostic accuracy and

moderate inter-observer reproducibility. The classification was published recently ¹²⁴ and it was still not used by other authors.

Prevalence

The studies have started from different populations, women undergoing hysteroscopy due to infertility ¹³⁵, infertile women undergoing *in vitro* fertilization (IVF) ¹²³, patients with singleton pregnancies with uterine anomaly diagnosed during pregnancy ¹³⁶, and women with adenomyosis ¹³³. Considering these different populations mentioned, the prevalence of T-shaped uterus varied from 0.2-10% in the different studies (Table 2). None of the studies that provided data to infer prevalence have mentioned the diagnostic criteria used to identify T-shaped uterus ^{133, 136} nor provided objective measurements for the diagnosis of T-shaped uterus ¹³⁵.

Etiology

Some authors mentioned that the etiology of T-shaped uterus is unknown ¹⁴², but it may also be primary ¹³⁵ or secondary to adhesions ^{2, 126, 135, 142}. One study has related T-shaped uterus to adenomyosis ¹³³ (Table 3). These studies have mentioned the causes above, but there is no research focusing on studying etiology.

Reproductive outcomes

T-shaped uterus is generally reported as related to worse reproductive outcomes. Nine studies have highlighted the association between subfertility and T-shaped uterus ^{122, 123, 126, 127, 129, 130, 138, 141,}

¹⁴². Some studies have included only patients with subfertility ^{122, 123, 126, 129, 130, 138}. Moreover, two studies have included women with unexplained subfertility ^{127, 129}, while three others have included women with other cause of subfertility ^{122, 126, 142}. Two studies provided a group of control for comparison (subfertile patients with normal uterus) ^{122, 123}. The prevalence of subfertility in T-shaped uterus varied between 45-74.1% ^{127, 141, 142}, which was considered to be higher than the 15% found in general population ¹⁴⁶.

Seven studies have included patients with a history of previous miscarriage and T-shaped uterus ^{122, 123, 126, 127, 139, 141, 147}, with the prevalence varying between 26-50%. Two studies have a group of control (patients with normal uterus) for comparison ^{122, 123} and it has been shown that the history of previous miscarriage was more common in patients with T-shaped uterus when compared to patients with normal uterus (one study showed a five-fold increase ¹²³). One study has included all patients with the previous history of miscarriage ¹³⁹.

Five studies have mentioned on recurrent miscarriage and T-shaped uterus ^{122, 123, 126, 127, 141}. Two studies has compared T-shaped with normal uterus, showing a higher prevalence of recurrent miscarriage in patients with T-shaped uterus: 20% vs. 10.2% ¹²³ and 17.6% vs. 10.8% ¹²². For the other studies it is possible to infer the higher prevalence of recurrent miscarriage in patients with T-shaped uterus: 18-33% ^{126, 127, 135, 141} vs. approximately 5% in the general population ¹⁴⁸. One study doesn't mention what they meant by repeated pregnancy loss ¹²³. The most definition used was two

or more spontaneous early pregnancy loss^{122, 126, 127} and two studies added a negative workup including karyotype analysis and antiphospholipid syndrome^{126, 127}. Two studies reported a very high rate of miscarriage per clinical pregnancy: > 80%^{129, 142} and two studies reported a high rate of preterm delivery related to T-shaped uterus: 20-85%^{129, 136}.

Seven studies reported prevalence of repeated implantation failure in patients presenting T-shaped uterus, which varied between 25-28%^{122, 123, 126, 127, 129, 130, 147}. The definition of repeated implantation failure was not uniform by the studies. Two studies have mentioned 2 or more failed IVF despite good quality embryos^{126, 127} found RIF in approximately 25% of the women; one study defined as the absence of pregnancy after ≥ 5 embryos transferred¹³⁰ and has included the totality of patients presenting RIF; one study defined it as ≥ 3 failed IVF cycles¹²²; one study described the number of failures by patient¹²⁹. One study didn't provide a definition for repeated implantation failure¹²³ but provided a group of control for comparison with prevalence of 10% in women with T-shaped uterus vs. 7% in women with normal uterus. The most accepted definition for repeated implantation failure in literature consists in three consecutive IVF attempts, in which one to two embryos of high-grade quality are transferred and that the expected prevalence of RIF is approximately 10%¹⁴⁹. Considering such 10% expected prevalence of three consecutive negative pregnancy tests following embryo transfer (the studies on T-shaped uterus didn't mention the quality of the embryos transferred, and therefore the expected prevalence would be higher), we found that one study showed a much higher

proportion of RIF in women with T-shaped uterus (35%)¹²², one study reported an expected proportion of RIF in women with T-shaped uterus (14%)¹²⁶, and one study reported a lower proportion of RIF in women with T-shaped uterus (3.6%)¹²⁹.

One study depicted a 15% prevalence of ectopic pregnancies in women with T-shaped uterus¹²⁹, much higher than the 1-2% expected in the general population¹⁵⁰.

Impact of surgery

Since there are some concerns that T-shaped uterus might be associated with poor reproductive outcomes, some authors are proposing hysteroscopic metroplasty as potential “treatment” for T-shaped uterus. Recently, a cascade of surgical reports on metroplasty of T-shaped uterus has been produced^{2, 122, 126, 127, 129, 132, 138, 139, 141, 142, 144, 147} (Table 5).

All the studies have mentioned improvement on reproductive outcomes after metroplasty for patients with T-shaped: 8 studies reported improvement on pregnancy rate^{122, 126, 127, 129, 138, 141, 142, 147}, 6 studies reported improvement on live birth rate^{2, 122, 127, 132, 138, 141, 144}, 5 studies reported reduction in miscarriage rate^{2, 127, 129, 142, 144}, 4 studies reported improvement on term delivery rate^{129, 138, 139, 142}, and 1 study reported reduction on ectopic pregnancy¹²⁹ (Table 6).

One study didn't ask for approval of the Institutional review board¹⁴¹. The surgical technique used for T-shaped uterus had a great variation across the identified studies; moreover, we didn't find any randomized controlled trial (RCT), only observational studies, and none of them had a control group

of untreated women for comparison. Four studies recognized the controversy of indicating metroplasty for women with T-shaped uterus ^{126, 130, 141, 144}. Nine studies recognized the need of prospective controlled trials to delineate a recommendation for hysteroscopic metroplasty for patients with T-shaped uterus ^{2, 122, 126, 127, 129, 130, 135, 139, 141}.

Eligible studies that didn't provide data for analysis

We couldn't evaluate reproductive outcomes of five studies because it was not possible to extract data for analysis. Fernandez et al. 2011 ² and Sukur et al. 2018 ¹⁴² have included patients who were not exposed to DES and also patients exposed to DES, and the outcomes were not reported separately. For two studies, we could only extract data regarding miscarriage per pregnancy ¹⁴² and previous miscarriage ¹³⁹ because they have reported the outcomes per pregnancy and not per participant. Two studies haven't report reproductive outcomes of the patients before metroplasty ^{132, 138}.

Di Spiezio Sardo et al. 2015 ¹³⁵, Ferro et al. 2018 ¹³⁰ and De Bruyn 2013 et al. ¹⁴³ included patients with other uterine malformations and the outcomes after surgical treatment were not reported separately for patients with T-shaped uterus ^{130, 135, 143} (**Table 7**). One study didn't ask for approval of the Institutional review board ¹³⁵.

Quality of the studies

Among the retrospective observational studies (**Supplemental Table 1**), most of them were considered as being of poor quality, except one that was rated as moderate ¹³⁶ (it was useful for the study of prevalence and clinical relevance of T-shaped uterus). The only identified diagnostic accuracy study was judged as having low risk of bias ⁸ (**Supplemental Table 2**). The same study was the only one assessing the reliability/agreement, being considered of moderate quality ^{110, 115} (**Supplemental Table 3**). All the studies assessing interventions were of poor quality (observational and quasi-experimental with before-after design).

Quality of the evidence

The quality of the evidence was very low: the quality of the evidence was downgraded two levels because only observational studies were included. Further downgrade should be performed because of important limitations of the included studies, including not having control group and high risk of bias. Moreover, the quality of the evidence should also be downgraded because of serious imprecision (studies with small sample size, median = 47; p25-75 = 19.5-80.5) and inconsistency on the results observed across studies.

DISCUSSION

The included studies in this systematic review have used different criteria for diagnosing T-shaped uterus and have used selected population (women with impaired reproductive outcomes). The prevalence of T-shaped uterus varied between 0.2-10%. The related causes of T-shaped uterus were

adhesions, adenomyosis and primary origin. The diagnosis was performed by different methods, and the most cited was 3D-US. There was no universally accepted definition for T-shaped uterus, although the most cited definition was the one from ESHRE-ESGE³. T-shaped uterus was related to worse reproductive outcomes (subfertility, miscarriage, preterm delivery, repeated implantation failure and ectopic pregnancy). Surgical treatment for T-shaped uterus has been proposed, and the available studies have reported a very optimistic improvement on reproductive outcomes after surgery as improvement on pregnancy rates, live birth rates, term delivery and reduction on miscarriage and ectopic pregnancy. This systematic review revealed that that available evidence for all the aspects of T-shaped uterus, particularly regarding the interventions is of very low quality.

Besides using an adequate diagnostic method for identifying T-shaped uterus, the criteria used for defining T-shaped uterus has big importance to assure that T-shaped uteri are identified correctly, and to avoid classification of normal uteri as being T-shaped. The ESHRE/ESGE definition for T-shaped uterus³, the most used by the studies may be unclear and misinterpreted by users, once the diagnosis is subjective and made by the impression of the observer. It is not clear what is 'narrow' and 'thickened' by measurable cut-offs. There is no mention to how the measurements of the uterus should be performed, what raise the doubt of the real occurrence of T-shaped uterus.

The reports regarding surgery was very uncommon before ESHRE-ESGE classification of congenital uterine anomalies, which has been pointed as potential iatrogenic etiologic factor, working

as a trampoline for promoting identification of a 'congenital anomaly' for normal uterus or benign conditions^{151, 152} and increasing the rates of prevalence and surgical treatment of patients with normal uterus^{153, 154}. The widening of the diagnostic boundaries of T-shaped uterus (before it was only DES-related anomaly) and active promoting its public awareness as disease with very poor prognosis may be an example of disease mongering for extend the use of hysteroscopy. For women presenting subfertility, current concerns are associated with selling unproved fertility treatment, which has been considered as unethical¹⁵⁵.

The definition proposed for T-shaped uterus by the CUME group¹²⁴ has a potential to facilitate the study of the prevalence, clinical relevance of T-shaped uterus and make possible to study the reproductive outcomes after surgical treatment. Despite being based in expert opinion, the CUME group developed a methodology to determine objective and measurable criteria, and there were not experts with known financial conflict of interests related to hysteroscopic equipment industries. Before CUME there was no measurable criteria for T-shaped uterus (Figure 2 ,3, 4).

None of the studies have included a group of untreated patients with expectant management to help on the study of natural history of disease and to evaluate the efficacy of the surgical intervention on reproductive outcomes. The lack of studies without any treatment indicates the high publication bias. The prevalence and impact of T-shaped uterus on reproductive outcome is still completely unknown, because the patients identified with T-shaped uterus have previous history of impaired

reproductive outcomes (patients from general population are not searched into uterine anomalies once they are asymptomatic).

Clinical implications of T-shaped uterus were assessed in the context of observational studies and poorly defined diagnostic criteria. In this review, the authors are not able to recognize the benefit of surgical treatment for T-shaped uterus despite of the very optimistic reported outcomes. Randomized trials including a group of untreated patients for comparison would be required to better study the efficacy of the surgical intervention on reproductive outcomes ^{2, 122, 126, 127, 129, 130, 135, 139, 141}. Despite of being a non-frequent condition, some authors found a number of patients with T-shaped uterus in a period of up to two years ^{123, 124, 126, 127, 135, 147}, what raises the question whether this condition is being overdiagnosed.

This systematic review has as an important limitation the inclusion of observational studies to evaluate reproductive outcomes after surgical treatment with the absence of a control group. The included studies didn't use the same diagnostic criteria for defining T-shaped uterus, and the surgical technique proposed for treating the condition varied along the studies. Also, the authors of this systematic review have published the most recent definition of T-shaped uterus ¹²⁴. To deal with the risk of bias related to the assessment of the quality of the studies, a neutral person was invited to review the data extracted and the judgement of the study and to review what was provided by the authors.

A review was published while we were already working on our review focused on reproductive outcomes following hysteroscopic metroplasty of patients with T-shaped uterus and previous history of poor reproductive outcomes ¹⁵⁶. The authors have included 15 articles in the review (8 published articles and 7 conference abstracts), from which we have also included 7 ^{2, 132, 135, 138, 139, 143, 144}. We have considered ineligible 7 studies (two studies have included patients exposed to DES ^{157, 158}, other two have included less than 10 women with T-shaped uterus ^{113, 159} and two because the authors have included patients with dysmorphic uterus, and haven't reported the outcomes separately for T-shaped uterus ^{160, 161} and one study because there was no mention to T-shaped uterus ¹⁶²). The remnant study was not included in the list of references of the review, so we couldn't identify it. The authors have concluded that hysteroscopic metroplasty is a simple procedure which can potentially improve reproductive outcomes, but the data is not robust.

For the future studies, there is a need for reliable and widely accepted criteria for diagnosing T-shaped uterus. Maybe the definition proposed by CUME will help on this. Studies evaluating whether T-shaped uterus is associated with worse reproductive outcomes will be needed (there are only published data regarding patients with T-shaped uterus and impaired reproductive outcomes, we do not know its relevance in general population). If there is an association to impaired reproductive outcomes, an RCT evaluating the effectiveness of metroplasty in improving the reproductive outcomes will be necessary before performing surgery in clinical practice. The challenges regarding

T-shaped uterus are the same of septate uterus: hysteroscopic septum resection for septate uterus is being performed worldwide for more than 30 years without supporting evidence^{163, 164}. Such approach causes unnecessary risks and imposes considerable financial burden on healthcare systems¹⁶⁵⁻¹⁶⁷. Another important issue of performing hysteroscopic metroplasty before we have good evidence about its effectiveness and safety is difficulties for recruiting participants on clinical trials when there is an overall agreement that the interventions is effective. The only concluded (but still unpublished) RCT on the topic needed more than 10 years to randomize 68 women¹⁶⁸; we hope their results will soon be available, providing some light to this important topic.

Conclusions

The true prevalence, clinical relevance, causes and associations of T-shaped uterus is still not known, as the available studies didn't use clear definition/criteria for the diagnosis of this condition. Additionally, little is known regarding the effect of the proposed intervention for T-shaped uterus, as hysteroscopic metroplasty; in addition to the problems regarding the proper diagnosis, there is no RCT and the available observational studies didn't even have a control group for comparison.

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For Peer Review

Figure 1: Flowchart of the study selection

Table 1 Diagnostic criteria used by included studies

STUDY	Diagnostic method and criteria	Observations
Boza et al. 2019 ¹²⁶	HSG and 3DUS HSG records were individually evaluated by two authors. Only when both authors were in agreement a diagnosis of T shaped was entertained. Analysis of the uterine shape by 3D-US was carried out in a standardized plane using the interstitial portions of the fallopian tubes as reference points. All were diagnosed with a T shaped uterus after a careful review of their HSG and 3D-TVS records by two independent observers.	It's not clear which criteria was used for diagnosing t-shape. The authors mention some measurements, but doesn't elicit the criteria for the diagnosis.
De Bruyn et al. 2013 ¹⁴³	Hysteroscopy + 2DUS uterus anomalies were subclassified based on the ESHRE-ESGE consensus classification of congenital uterus anomalies. To differentiate T-shaped uterus from dysmorphic uterus (a combination of T-shaped plus septate uterus), a measurement of fundal size was performed by sagittal plane of 2DUS	Subjective diagnosis They didn't use 3DUS or MRI
Di Spiezo Sardo et al. 2015 ¹³⁵	Hysteroscopy + 3DUS Hysteroscopy- presence of an enlarged distance between the tubal ostia; with a correlation of two-thirds uterine corpus and one-third cervix (T-shaped uterus); Interstitial distance (i.e. distance between the two tubal ostia) as well as the transverse diameter at the level of isthmus 3DUS-distance between tubal ostia (IO), the transversal diameter at the isthmus (I), the I/O ratio as well as the thickness of the uterine side walls and the depth of the healthy myometrium up to the serosa	The authors declare that used the ESHRE/ESGE definition in prospective study performed between June 2011 and March 2012. The ESHRE/ESGE definition of T-shaped uterus was unknown in the study period. The study was experimental regarding a surgical procedure that has not its advantages well established, and it was not approved by the institutional review board.
Di Spiezo Sardo et al. ¹⁴¹	2019 hysteroscopy + 3DUS narrow uterine cavity due to thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 cervix hysteroscopy- enlarged distance between the tubal ostia, a narrow uterine cavity or abnormally elongated cervical canal. 3D US-Evaluation of uterine architecture was carried out using the interstitial portions of the fallopian tubes as reference points. The distance between tubal ostia (IO), the transversal diameter at the isthmus (I), the I/O ratio as well as the thickness of the uterine side walls and the depth of the healthy myometrium up to the serosa were also measured.	Although they mention that have used the definition of ESHRE/ESGE for diagnosing T-shaped uterus, it is still a subjective diagnosis. The study period was 2011-2017. The use of ESHRE/ESGE definition was declared, but the classification was unknown between 2011-2013. The measurements proposed by 3DUS are used for comparison between before and after the metroplasty, not for diagnosing T-shaped uterus. The study is regarding a surgical procedure that has not its advantages well established and not recommended by any international scientific society focused on reproductive medicine and surgery. The study was not approved by the institutional review board. The study states that before enrolment, the purpose of the study was

Ducellier Azolla et al. 2018 ¹⁴⁴	HSG and/or 3DUS and/or hysteroscopy Hysterosalpingography enabled the size and shape of the uterine cavity to be determined along with tubal patency. Three-dimensional confirmed whether the T-shaped appearance of the uterine cavity was due to a subcornual stricture (It enables precise evaluation of myometrial subcornual thickness (which should not be less than 12 mm and projection of the requisite incisional depths) hysteroscopic diagnosis was based on the criteria for uterine dysmorphism drawn up by the ESHRE/ESGE	explained clearly, and all patients received detailed information about the study, to which they gave their consent, but it questionable considering its retrospective design. As the study include patients along 24 years, certainly the same diagnostic criteria and methods were not used along all these years.
Exacoustos 2015 et al. ¹⁴⁵	3DUS following measurements were taken: 1) fundal cavity width (W1) (the distance between the two internal tubal ostia), 2) width of uterine cavity at corpus-isthmic level (W2), 3) uterine fundal wall thickness (M) (the distance from interostial line and the external uterine serosa), 4) the lateral angle between the corpus-isthmic cavity and the two fundal endometrial layers (A right; A left), 5) in case of cavity fundal indentation the indentation length (L) (the distance from the tip of the fundal indentation to the interostial line) and fundal indentation angle (a) (the angle between the two endometrial layers). The mean measurements of mean A (A right + A left/2) and W1/W2 ratio was significantly different in the dysmorphic uteri compared to normal.	The study has compared T-shaped uterus to septate and normal uterus. The study has included only 25 patients
Fernandez et al. 2011 ²	2DUS, 3DUS and MRI US measure the bulging of the uterine side walls, their thickness and the depth of the healthy myometrium up to the serosa.	The authors were not clear regarding the diagnostic criteria used.
Ferro et al. 2018 ¹³⁰	Hysteroscopy Subjective	The diagnosis of T-shaped uterus was inadequate, based on hysteroscopic findings and subjective. Also, the authors describe that many of these uteri also had some degree of a fundal notch (it is possible that they have included normal, arcuate and septate uterus).
Giacomucci et al. 2011 ¹³⁹	Hysteroscopy Hypoplastic and cavity with arched base, constriction rings around the proximal and medial uterine segment	By hysteroscopy it is not possible to evaluate if there is thickened lateral walls, and differentiation between obvious uterine morphologies is not reliable; nothing is mentioned regarding DES exposure

Haydardedeoglu et al. 2018 ¹²⁹	HSG- condensed lateral side uterine cavity observed using a properly performed HSG, in which the traction to the uterus was sufficient to expose the normal plain of the uterine cavity	The diagnosis by HSG is subjective. 3D US was not performed
Ludwin et al. 2019 ¹²⁴	3D-US The diagnosis was subjective (the most voted option by 15 experts) lateral indentation angle < 130° lateral indentation depth > 7 mm T-angle ≤ 40° 3D-US or HSG Narrow endometrial cavity	Measurements performed by highly trained raters and using a single 3D ultrasound dataset. Only datasets with subjectively detected lateral indentation without any other subjectively detected anomaly (possibility of selection bias). Internal os was used as a reference point for the lateral indentation depth (the identification of the internal os might be difficult to determine) The authors were not clear regarding the diagnostic criteria used.
Mounir et al. 2012 ¹³⁸	3D-US	The study mentions the measurements and compare T-shaped to normal and intermediate uterus, but the study is not clear regarding criteria to diagnose T-shaped uterus.
Neal et al. 2019 ¹²³	The diagnosis was subjective (the most voted option by 5 observers: normal, intermediate, T-shaped) The study suggests measurements: interostial distance, isthmic diameter, diameter at the internal cervical os, virtual organ computer-aided analysis rendering of endometrial volume. The study mention that T-shaped uterine cavity has increased interostial distance and decreased isthmic diameter when compared to normal uterus. Endometrial volume was lower in women with intermediate uterine cavity morphology, relative to normal.	
Pacheco et al. 2019 ¹²⁷	3D-US and hysteroscopy Uterine wall thickness is the distance between the interostial line and external uterine profile at the mid-coronal plane of the) By hysteroscopic view there is isthmic and subcornual strictures, associated with hypoplastic uterine cavity.	The authors propose a measurement, but don't provide cut-off or strict diagnostic criteria. The description for measuring uterine wall thickness is subjective (mid-coronal plane; but where to measure?).
Sukur et al. 2018 ¹⁴²	HSG and MRI Narrow uterine cavity due to thickened lateral walls.	The authors don't mention objective criteria to identify T-shaped uterus There is no mention to DES exposure by the included patients
Uyar et al. 2019 ¹²²	HSG and/or 3DUS Narrow uterine cavity due to thickened lateral walls	ESHRE-ESGE criteria is subjective. The study period was 2011-2016. The use of ESHRE/ESGE definition was declared, but the classification was unknown between 2011-2013. There was no mention to who made the diagnosis. Diagnosis by HSG is inadequate.

ESHRE-ESGE definition: T-shaped uterus is characterized by a narrow uterine cavity due to thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 cervix.

For Peer Review

Table 2 Prevalence of T-shaped uterus reported on the included studies.

STUDY	PREVALENCE	Population	Observations
Di Spiezio Sardo et al. 2015 ¹³⁵	12/324 (4%)	Women undergoing hysteroscopy due to infertility	It is not known the proportion of T-shaped uterus in the excluded women.
Fox et al. 2014 ¹³⁶	10/4,473 (0.2%)	Singleton pregnancies > 22 weeks diagnosed with uterine anomaly during pregnancy	
Neal et al. 2019 ¹²³	10/648 (1.5%)	Infertile patients undergoing IVF	The study mentions the measurements and compare T-shaped to normal and intermediate uterus, but the study is not clear regarding criteria to diagnose T-shaped uterus.
Puente et al. 2016 ¹³³	25/248 (10%)	Women with adenomyosis	The authors use the term pseudo T-shaped, in which there a similar appearance to T-shaped uterus, but don't cite objective criteria do diagnose it.

Table 3 Reported associations/causes of T-shaped uterus

Primary condition	Ducellier Azola et al. 2018 ¹⁴⁴ , Di Spiezio Sardo et al. 2015 ¹³⁵ and Neal et al. 2019 ¹²³
Consequence of another condition	
Adhesions	Boza et al. 2019 ¹²⁶ , Di Spiezio Sardo et al. 2015 ¹³⁵ , Fernandez et al. 2011 ² , Sukur et al. 2018 ¹⁴² and Neal et al. 2019 ¹²³
Adenomyosis	Puente et al. 2016 ¹³³

For Peer Review

Table 4 Association of T-shaped uterus with clinical conditions.

Study	Prevalence in T-shape uterus	Prevalence in normal/arcuate uterus	Conclusion
Subfertility			
Boza 2019 et al. ¹²⁶	56/56 (100%)	NR	High risk, no comparison
Di Spiezio Sardo et al. 2019 ¹⁴¹	92/124 (74.1%)	NR	High risk, no comparison
Ferro et al. 2018 ¹³⁰	190/190 (100%)	NR	High risk, no comparison
Haydardedeoglu et al. 2018 ¹²⁹	272/272 (100%)	NR	High risk, no comparison
Mounir 2012 ¹³⁸	88/88 (100%)	NR	High risk, no comparison
Neal et al. 2019 ¹²³	10/10 (100%)	472/472 (100%)	
Pacheco et al. 2019 ¹²⁷	27/60 (45%)	NR	High risk, no comparison
Sukur et al. 2018 ¹⁴²	43/78 (55.1%)	NR	High risk, no comparison
Uyar et al. 2019 ¹²²	74/74 (100%)	148/148 (100%)	
Previous miscarriage			
Boza et al. 2019 ¹²⁶	22/56 (39.2%)	NR	High risk, no comparison
Di Spiezio Sardo et al. 2019 ¹⁴¹	32/124 (25.8%)	NR	
Ferro et al. 2009 ¹⁴⁷	4/18 (22%)	NR	
Giacomucci et al. 2011 ¹³⁹	17/17 (100%)		
Neal et al. 2019 ¹²³	5/10 (50%)	48/472 (10.2%)	T-shaped = Higher risk
Pacheco et al. 2019 ¹²⁷	20/60 (33.3%)	NR	High risk, no comparison
Uyar 2019 ¹²²	19/74 (25.7%)	25/148 (16.9 %)	same risk
Recurrent miscarriage			
Boza et al. 2019 ¹²⁶	10/56 (17.8%)	NR	High risk, no comparison

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Di Spiezio Sardo et al. 2019 ¹⁴¹	32/124 (25.8%)	NR	High risk, comparison	no
Neal et al. 2019 ¹²³	2/10 (20%)	48/472 (10.2%)	T-shaped = Higher risk	no
Pacheco et al. 2019 ¹²⁷	20/60 (33.3%)	NR	High risk, comparison	no
Uyar et al. 2019 ¹²²	13/74 (17.6%)	16/148 (10.8 %)	Same risk	
Miscarriage per pregnancy				
Sukur et al. 2018 ¹⁴²	63/75 (84%)	NR	High risk, comparison	no
Haydardedeoglu et al. 2018 ¹²⁹	93/110 (84.5%)	NR	High risk, comparison	no
Preterm delivery				
Fox et al. 2014 ¹³⁶	2/10 (20%)			
Haydardedeoglu et al. 2018 ¹²⁹	93/110 (84.5%)	NR	High risk, comparison	no
Repeated implantation failure				
Boza et al. 2019 ¹²⁶	8/56 (14.1%)		High risk, comparison	no
Ferro et al. 2009 ¹⁴⁷	5/18 (28%)		High risk, comparison	no
Ferro et al. 2018 ¹³⁰	190/190 (100%)	NR	High risk, comparison	no
Haydardedeoglu et al. 2018 ¹²⁹	10/272 (3.6%)	NR	T-shaped = Higher risk	no
Neal et al. 2019 ¹²³	1/10 (10%)	31/472 (6.6%)	High risk, comparison	no
Pacheco et al. 2019 ¹²⁷	16/60 (26.6%)	NR	High risk, comparison	no
Uyar et al. 2019 ¹²²	35.1 (26/74%)	26/148 (17.6%)	T-shaped= Higher risk	
Ectopic pregnancy				
Haydardedeoglu et al. 2018 ¹²⁹	17/110 (15.5%)	NR	T-shaped=Higher risk	

General prevalence of infertility is about 15%¹⁶⁸; general prevalence of previous miscarriage is near 15%¹⁷⁰; the prevalence of recurrent miscarriage (two or more losses before 24 weeks of pregnancy) is 5%¹⁴⁸; the prevalence of repeated implantation failure (after three consecutive IVF attempts, in which one or two high-grade quality embryos were transferred in each cycle) is 10%¹⁴⁹; preterm delivery rate in general population is 5-10% in singletons and 40-60% in multiples¹⁷¹; Ectopic pregnancy in general population occurs in 1-2%¹⁵⁰.

Table 5 Studies assessing the effect of interventions for T-shaped uterus.

Study	Intervention and description	Outcomes and Observations
Boza et al. 2019 ¹²⁶	Hysteroscopic metroplasty The surgical technique consisted of making two lateral incisions in the isthmic area of the uterine sidewalls and one incision when necessary to the fundal area.	n=56 (32 patients with unexplained infertility, 14 patients with RIF, 10 patients with RPL). Patients with long standing unexplained infertility, 9/32 conceived spontaneously and 11/32 with IVF. Patients with RIF, 4/14 conceived spontaneously and 5/14 conceived after IVF. 66% of the patients conceived spontaneously or after IVF. The procedure has increased the volume of the uterine cavity. The authors recognize the controversy of surgical management of T-shaped uterus and the beneficial effect of hysteroscopic metroplasty. The study doesn't let clear primary endpoints. There wasn't a control group for comparison.
Di Spiezio Sardo et al. 2019 ¹⁴¹	Hysteroscopic metroplasty Longitudinal lateral incisions were performed on the fibro-muscular constriction rings in the isthmic area and in case the presence of a tubular cavity also on the anterior and posterior uterine walls.	124 out of 214 included patients had T-shaped uterus. Clinical pregnancy rate was 76.6% (95/124), miscarriage rate per clinical pregnancy was 24.2% (23/95), ongoing pregnancy/live birth rate per patient was 58.1% (72/124). 83 patients conceived spontaneously, 2 patients conceived after IUI and 39 patients conceived after IVF. After 5 years, the overall clinical pregnancy rate was 72.9% (156/214) and the live birth rate was 80.1% (125/156). Contacting the author we could obtain the reproductive outcomes for patients with T-shaped uterus separately. This is a retrospective study; approval by the institution review board was not obtained. There isn't a control group for comparison.
Ducellier Azolla et al. 2018 ¹⁴⁴	Hysteroscopic metroplasty The myometrium was laterally incised on each side, perpendicular to the uterine wall without exceeding an incision depth of 7 mm.	67 out of the 112 included patients were exposed to DES. The results are not reported separately for patients who were not exposed to DES. There was 100 of pregnancies after metroplasty. The live birth rate increased: 4 (2.5%) vs. 60 (60%), p<0.05. The miscarriage rate reduced: 126 (78.3%) vs. 22 (22%), p<0.05. There was an increase in the number of live births statistically significant and significant reduction in the number of early spontaneous miscarriage. Also, increase in the rate of term deliveries. The study included patients who underwent treatment along 24 years (expected different equipment and different technique). Data are not complete. There isn't a control group of untreated patients for comparison.
Fernandez et al. 2011 ²	Hysteroscopic metroplasty Two incisions in the lateral walls are made from the fundus to the isthmus, under direct vision, perpendicular to the lateral wall. The depth of incision does not exceed 5–7 mm.	63 out of 97 included patients were exposed to DES. Reproductive outcomes are not reported separately for patients with T-shaped uterus not exposed to DES. Forty-eight women (49.5%) became pregnant after metroplasty. The live birth rate per pregnancy increased from 0% to 73%, and the miscarriage rate fell from 78 to 27% (p<0.05). Number of miscarriages and ectopic pregnancies diminished after surgery treatment; number of term deliveries and live births has increased. There isn't a control group for comparison.
Ferro et al. 2009 ¹⁴⁷	Hysteroscopic metroplasty Repeated incisions especially in the mid cavity, where the myometrium takes the	N=18 patients with T-shaped uterus (4 of them had previous miscarriages and 5 failure after RIF; for the other 9 patients nothing is mentioned; 2 patients dropped-out). 6/16 women had spontaneous pregnancies (1 biochemical pregnancy, 1 neonatal death and 4 healthy newborns). Mean gestational age was 37.6 weeks at birth. 9 women achieved pregnancy after

	form of constriction rings, and also in the arcuate fundus.	IVF (6 had a term delivery, 2 were preterm and 1 had a miscarriage). Grouping assisted and natural reproduction together, 88% became pregnant in a 2-year period. The study doesn't mention the diagnostic criteria used. There was not a control group for comparison. It's not clear whether the patients were exposed to DES.
Giacomucci et al. 2011 ¹³⁹	Hysteroscopic metroplasty the uterine side walls were incised until a normal uterine cavity was achieved.	n=17 patients with T-shaped uterus and previous recurrent miscarriage. Term delivery rate has raised from 0 to 66,7% after hysteroscopic metroplasty intervention.
Haydardedeoglu et al. 2018 ¹²⁰	the lateral side walls were cut using a Bipolar resectoscope until the tubal orifice was visible from the isthmus.	There isn't a control group for comparison. Diagnosis made by hysteroscopy. N=272 infertile patients. Before metroplasty, the patients had high miscarriage rate (84.5%), had previous ectopic pregnancy (15.5%), had zero preterm and term delivery rate. After metroplasty, miscarriage rate was 49.6%, ectopic pregnancy was uncommon (1.48%), and there was an increase in preterm delivery rate (2.7%) and term delivery rate (85.1%). The diagnosis of T-shaped uterus was made by hysterosalpingography. There isn't a control group for comparison.
Mounir et al. 2012 ¹³⁸	Hysteroscopic metroplasty Postmenstrual operative 90-degree resectoscope was used in all of them with monopolar current 25-30 V and glycine as a distension media	Spontaneous pregnancy: 49/88 became pregnant up to two years; 3/49 had miscarriage (they already had a previous miscarriage); 2/49 preterm deliveries. Assisted pregnancies: 16 underwent ICSI; 9/16 became pregnant; 5/9 twin pregnancies; 4/9 live birth; 1/9 preterm; 3/9 term delivery. Overall: 55/88 became pregnant (65.9%). The author concludes that the metroplasty has marked success in the treatment of infertile women in addition to its effect in term pregnancies. The study is not clear about diagnostic criteria for T-shaped. The diagnosis of T-shaped uterus was subjective. There isn't a control group for comparison nor mention to previous reproductive outcomes.
Pacheco et al. 2019 ¹²⁷	Hysteroscopic metroplasty Two lateral incisions at the lateral uterine sidewall operative scissors, from the isthmus to the uterine fundus. The maximum incision depth was 7 mm. the aim was to visualize both the tubal ostia from the isthmus, and subcornual strictures were interrupted.	n=60 patients willing for pregnancy. Fifty out of 60 women became pregnant, with an overall clinical pregnancy rate after metroplasty of 83.3%. The live birth rate was 76% (n = 38/50). The cesarean section rate was 26.3% (n = 10/38). Considering the other 12 clinical pregnancies, six pregnancies are ongoing, and 6 were miscarriages (miscarriage rate was 12. 6% n=6/50). The abortion rate decreased from 100% of pregnancies before to 12% (n = 6/50) after the metroplasty (p < 0.001). The study doesn't mention objective diagnostic criteria for T-shaped. There is not a control group for comparison.
Soekoer et al. 2016 ¹³²	Hysteroscopic metroplasty surgeries were performed with an operative hysteroscope, fitted with a monopolar hook cautery.	N=78 patients with T-shaped uterus. There is no mention to which diagnostic method was used nor to diagnostic criteria for T-shaped uterus. The study was published as a conference abstract. There is no mention to how many patients had previous history of subfertility or recurrent miscarriage. The live birth rate increased from 8% (6 per 75 pregnancies) to 75.6% (28 per 37 pregnancies) after hysteroscopic metroplasty (P<0.001).
Sukur et al. 2018 ¹⁴²	Hysteroscopic metroplasty The resection of lateral side walls was performed till a triangular and symmetric cavity is achieved. The lateral side walls in T-shaped uterus were incised through	The chance of live birth significantly increased after hysteroscopic correction class U1a (OR 35.7; 95% CI, 11.6-109.9; P < .001). The mean gestational age at birth was 37.3 + 4.0 weeks. Miscarriage decreased from 63 to 7 after the procedure (significant); preterm birth was not different comparing before and after surgery. Term delivery raised from 3 to 23. There was not a control group for comparison. There is no mention to DES exposure by the included patients.

Uyar et al. 2019 ¹²²	<p>the tubal ostia to the cervix, and the depth of the incision was between 5 and 7 mm.</p> <p>Hysteroscopic metroplasty</p> <p>The lateral side walls in T-shaped uterus were incised through the tubal ostia to the cervix.</p>	<p>Only 4.1% (3/74) of patients undergoing metroplasty delivered beyond 20 weeks of gestation compared to 18.2% (20/148) in the control group ($p < 0.05$) (control group- no uterine anomaly). Both number of previous unsuccessful ART cycles and number of patients with ≥ 3 unsuccessful IVF cycles were significantly higher in the metroplasty group. Endometrial thickness was statistically lower in the metroplasty group. Rates of implantation (28.1% vs 35.8%, $p > 0.05$), pregnancy (54.1% vs 56.8%, $p > 0.05$), clinical pregnancy (43.2% vs 50.7%, $p > 0.05$) and live birth (35.1% vs 46.6%, $p > 0.05$) were similar between the metroplasty and the control groups (obstetrics outcomes of patients with T-shaped uterus were comparable to patients with normal uterus), respectively. There was a non-significant trend for a higher rate of miscarriage (18.8% vs 8%, $p > 0.05$) in the metroplasty group when compared to the control group.</p> <p>The protocols used for IVF varied, also the number and days of evolution of the transferred embryos. Ideally, the control group would be composed by women with T-shaped uterus in expectant management.</p>
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Table 6 Summary of the conclusions of the studies assessing hysteroscopic metroplasty for improving reproductive outcomes in women with T-shaped uterus.

	Pregnancy	Live birth	Miscariage	Term delivery	Ectopic
Boza et al. 2019 ¹²⁶	improved				
Di Spiezio Sardo et al. 2019 ¹⁴¹	improved	improved	not clear		
Ducellier-Azolla et al. 2018 ¹⁴⁴		improved	Reduced		
Fernandez et al. 2011 ²		improved	Reduced		
Ferro et al. 2009 ¹⁴⁷	improved			improved	
Giacomucci et al. 2011 ¹³⁹			Reduced	improved	
Haydardedeoğlu et al. 2018 ¹²⁹	improved		Reduced	improved	reduced
Mounir 2012 ¹³⁸	improved	improved		improved	
Pacheco et al. 2019 ¹²⁷	improved	improved	Reduced		
Soekoer et al. 2016 ¹³²		improved			
Sukur et al. 2018 ¹⁴²	improved		Reduced	improved	
Uyar et al. 2019 ¹²²	improved	improved	not clear		

Table 7: Eligible studies that didn't provide data for analysis

Study	Intervention and description	Outcomes and Observations
De Bruyn et al. 2013 ¹⁴³	Hysteroscopic metroplasty The technique of the intervention is not described	The study has included 38 patients with T-shaped uterus and 18 patients with dysmorphic uterus (a combination of T-shaped and subseptate uterus). The outcomes were not reported separately for T-shaped uterus. 81% of the included patients became pregnant in three months (the results are not reported separately for T-shaped uterus). The study was published as an abstract. Methodology is not clear.
Di Spezio Sardo et al. 2015 ¹³⁵	Hysteroscopic metroplasty Two incisions on the fibro-muscular constriction rings in the isthmic area of the uterine side walls. Other incisions on the anterior and posterior uterine walls from the fundus up to the isthmus. The depth of the incisions did not exceed 5-6 mm.	The study has included 12 patients with T-shaped uterus and 18 patients with tubular-shaped uterus. The procedure has increased the volume of the uterine cavity, except in one patient. Clinical pregnancy rate 17/30 (57%); live birth rate 12/17 (71%); spontaneous abortion rate 5/17 (29%); term delivery rate 11/17 (65%). This is an observational study. Outcomes are not reported separately for T-shaped uterus. There isn't a control group for comparison. Study was not approved by the Institution review Board.
Ferro et al. 2018 ¹³⁰	Hysteroscopic metroplasty Incision at the level of the prominent lateral myometrial walls at nine and three hours from the isthmic region and in the direction towards the tubal orifices. Cut in the prominent fundus of cavity in uterus T shape with fundal indentation.	n=190 patients with T-shaped uterus or infantilis uterus. Results were not reported separately. The total clinical pregnancy rate was 80.0% (152/190), the live birth rate 77.3% (143/190) and the abortion rate was 11.1% (17/152). At 12 months, the clinical pregnancy rate was 76.3%. Ninety-six percent of gestations were achieved between 1 – 3 IVF cycles. Thirty-four out of 152 pregnant women (21 twin and 13 singleton pregnancies) resulted in preterm delivery (34/152, 22.3%). Eighty-six patients (56.5%) were delivered by cesarean section. The study includes patients aged between 25-48 years old (a wide age group), and the diagnosis of T-shaped uterus was inadequate, based on hysteroscopic findings and subjective. The authors mention that many of these uteri also had some degree of a fundal notch (we may ask if they were really T-shaped). There is a lack of a control group.

Supplemental Table 1 Quality of the included observational studies according to Newcastle-Ottawa Scale (NOS) .

Study	Selection		Selection of the non-exposed cohort	Ascertainment of Exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability	Outcome		Judgment
	Representativeness of the exposed cohort*	Comparability of the cohorts on the basis of the design or analysis controlled for confounders*					Assessment of the outcome**	Was follow up long enough for outcome to occur	
Impact of metroplasty in T-shaped uterus									
Boza et al. 2019 ¹²⁶	One star Women with infertility, recurrent implantation failure (RIF), and/or recurrent pregnancy loss (RPL) who presenting T-shaped uterus	There isn't a non-exposed cohort	One star Metroplasty	One star Clinical pregnancy Live birth rate Spontaneous abortion	All the subjects underwent metroplasty	For clinical pregnancy- US For live birth rate/spontaneous abortion- no description	One star no losses	One star One year	Total = 5 Selection: 3 stars Comparability: N/A Outcome/exposure: 2
De Bruyn et al. 2013 ¹⁴³	One star Women presenting dysmorphic uterus	There isn't a non-exposed cohort	One star Metroplasty	The outcomes are not mentioned ("to look at the reproductive performance before and after the hysteroscopic surgery. The secondary aim is to review the obstetric outcomes after surgery")	All the subjects underwent metroplasty	Not mentioned	Not mentioned	Not mentioned	Total = 2 Selection: 2 stars Comparability: N/A Outcome/exposure: 0

Di Spizio Sardo et al. 2015 ¹³⁵	One star Women with history of primary infertility, repeated miscarriages (>2) or severe preterm delivery (<25 weeks) presenting with dysmorphic uterus (T-shaped or tubular shaped/infantilis uterus).	There isn't a non-exposed cohort	One star Metroplasty	One star Clinical pregnancy Term delivery Spontaneous abortion	All the subjects underwent metroplasty	Self-report (data obtained by telephone interview monthly)	One star Fifteen months	One star No losses	Total = 5 Selection: 3 stars Comparability: N/A Outcome/exposure: 2 stars
Di Spizio Sardo et al. 2019 ¹⁴¹	One star Women with history of primary unexplained infertility or repeated miscarriage	There isn't a non-exposed cohort	One star Metroplasty	One star Clinical pregnancy rate Miscarriage Term delivery Delivery > 34 weeks Live birth rate (it is presumed that the patients didn't have live birth rate before the treatment because the study included patients with primary or repeated miscarriage)	All the subjects underwent metroplasty	Clinical chart and contact by telephone	One star 60 months	One star No losses	Total=5 Selection: 3 stars Comparability: N/A Outcome/exposure: 2 stars
Ducellier-Azzola et al. 2018 ¹⁴⁴	One star Women with infertility and recurrent miscarriages	There isn't a non-exposed cohort	One star Metroplasty	One star Live birth	All the subjects underwent metroplasty	Data were complete for 60, incomplete for 43 and missing for	Not mentioned	One star The study was unaware of	Total = 4 Selection: 3 stars Comparability: N/A

	presenting T-shaped uterus			Early spontaneous miscarriages Term deliveries		9 of these patients. Characteristics of the patients were obtained from their medical dossiers. Obstetrical characteristics were collected by telephone contact with the Patients or by contacting the physician	the outcome of four pregnancies (6%).	Outcome/exposure: 1 star
Fernandez et al. 2011 ²	One star Women with T-shaped uterus with a history of primary infertility, recurrent abortion or preterm delivery before 30 weeks, with or without live birth.	There isn't a non-exposed cohort	One star Metroplasty	One star Miscarriage Ectopic pregnancy Preterm delivery Term delivery Live birth	All the subjects underwent metroplasty	Not mentioned	One star Thirty-nine months	Total = 5 Selection: 3 stars Comparability: N/A Outcome/exposure: 2 stars
Ferro et al. 2009 ¹⁴⁷	One star Patients with implantation failure or recurrent pregnancy loss presenting T-shaped uterus	There isn't a non-exposed cohort	One star Metroplasty	One star Pregnancy achievement Miscarriages Deliveries Perinatal health	All the subjects underwent metroplasty	Not mentioned	One star Two years	Total = 4 Selection: 2 stars Comparability: N/A Outcome/exposure: 2 stars
Ferro et al. 2018 ¹³⁰	One star Infertile patients with recurrent implantation failure (defined for this study as ≥ 5 pre-embryos transferred), and posterior	There isn't a non-exposed cohort	One star Metroplasty	One star Live birth rate	All the subjects underwent metroplasty	Not mentioned (they only mention a visit of follow-up 2 months after the procedure)	One star Not mentioned, but patients were followed-	Total: 4 Selection: 3 stars Comparability: N/A Outcome/exposure: 1 star

	hysteroscopic diagnosis of a dysmorphic uterus [including T-shaped uteri]	There isn't a non-exposed cohort	One star Metroplasty	One star Term delivery rate was 0 before metroplasty for patients with T-shaped uterus	All the subjects underwent metroplasty	One star Medical records	Not mentioned, but some patients had live birth	No losses, but some patients are still trying to get pregnant	Total = 4 Selection: 2 stars Comparability: N/A Outcome/exposure: 2 stars
Giacomucci et al. 2011 ¹³⁹	One star Patients with uterine malformation and two or more spontaneous abortion	There isn't a non-exposed cohort	One star Metroplasty	One star Preterm delivery Term delivery	All the subjects underwent metroplasty	delivery registry from our hospital database and via telephone interviews	Not mentioned, but some patients had live birth	Not mentioned	Total=3 Selection: 3 stars Comparability: N/A Outcome/exposure: 0
Haydardedeoglu et al. 2018 ¹²⁹	One star Unexplained infertility	There isn't a non-exposed cohort	One star Metroplasty	The authors don't mention previous obstetrics outcomes (live birth rate, clinical pregnancy rate, term delivery, preterm delivery)	All the subjects underwent metroplasty	Not mentioned	One star 36 months	One star 11 out of 88 patients (12.5%)	Total: 4 Selection: 2 stars Comparability: N/A Outcome/exposure: 2 stars
Mounir 2012 ¹³⁸	One star Women with primary infertility	There isn't a non-exposed cohort	One star Metroplasty	The authors don't mention previous obstetrics outcomes (live birth rate, clinical pregnancy rate, term delivery, preterm delivery)	All the subjects underwent metroplasty	Medical records and follow-up visits after the procedure	One star At least one year after metroplasty	Three out of 63 women tried to conceive after metroplasty (1 had colon cancer, 1	Total=4 Selection: 2 stars Comparability: N/A Outcome/exposure: 2 stars
Pacheco et al. 2019 ¹²⁷	One star Patients with primary unexplained infertility, repeated IVF failure (RIF) or recurrent spontaneous miscarriages	There isn't a non-exposed cohort	One star Metroplasty	The authors don't mention previous obstetrics outcomes (live birth rate, clinical pregnancy rate, spontaneous miscarriages rate)	All the subjects underwent metroplasty	Medical records and follow-up visits after the procedure	One star At least one year after metroplasty	Three out of 63 women tried to conceive after metroplasty (1 had colon cancer, 1	Total=4 Selection: 2 stars Comparability: N/A Outcome/exposure: 2 stars

									had peritonitis due to diverticulitis, 1 has psychological problems)		Total= 4 Selection: 3 stars Comparability: N/A Outcome/exposure: 1 star
Soekoer et al. 2016 ¹³²	One Star Patients with T-shaped uterus with a history of primary infertility, recurrent miscarriage, preterm delivery	There isn't a non-exposed cohort	One star Metroplasty	One star Live birth rate increased from 8% (6 per 75 pregnancies) to 75.6% (28 per 37 pregnancies)	All the subjects underwent metroplasty	Hospital database and phone interviews when necessary.	One star The mean follow-up period of the patients was 27 months (range: 12-84 months).	Not mentioned			
Sukur et al. 2018 ¹⁴²	One star Women with history of primary infertility, recurrent miscarriage, or preterm delivery	There isn't a non-exposed cohort	One star Uterine malformation	One star Miscarriage was significantly more common than after surgery, and preterm delivery and term delivery were significantly less common than after surgery	All the subjects underwent metroplasty	Patients who could not be reached by phone (n=7) and who did not have a try for pregnancy after surgery (n=33) were not included into the postoperative evaluation for reproductive outcome.	One star yes median follow-up period for all patients was 42 months (range 12-84 months). At	Losses: 7 patients who could not be contacted by phone and 33 patients who haven't tried to conceive.			Total = 4 Selection: 3 stars Comparability: N/A Outcome/exposure: 1 star

Impact of T-shaped uterus

Fox et al. 2014 ¹³⁶	One star Women with a uterine anomaly diagnosed prior to or during pregnancy.	One star Unexposed group, we chose an equal number of randomly selected singleton pregnancies > 22 weeks delivered by our practice over the study period.	One star Uterine malformation	One star Preterm birth, spontaneous preterm birth, indicated preterm birth, low birth weight, SGA, preeclampsia, malpresentation and cesarean delivery	One star b	One star Medical records	One star Until delivery	Not mentioned 0	Total = 7 Selection: 4 stars Comparability: 1 Outcome/exposure: 2 stars
Neal et al. 2019 ¹²³	One star Infertile patients undergoing a single blastocyst transfer with T-shaped uterus	One star Infertile patients undergoing a single blastocyst transfer with normal/intermediate uterus	One star Uterine malformation (T-shaped uterus)	Live birth rate The parity of patients with normal and intermediate uterus is higher than the patients with T-shaped uterus (before undergoing embryo transfer)	The three groups (normal, intermediate and T-shaped) were different according to previous parity, previous failed transfer and endometrial thickness on the day of embryo transfer	Not mentioned	One star Until delivery	One star 10 were excluded due to not performing embryo transfer	Total: 5 Selection: 3 stars Comparability: 0 Outcome/exposure: 2 stars
Uyar et al. 2019 ¹²²	One star Infertile patients who underwent hysteroscopic correction for T-shaped uterus	One star Women with infertility and normal uterus	One star Metroplasty	Live birth Pregnancy loss	C Intervention group had T-shaped and underwent metroplasty	Medical records Missing data was completed through interview of the patients by phone	not mentioned	Not mentioned	Total: 3 Selection: 3 stars Comparability: 0 Outcome/exposure: 0

[illegible]

* a-The study controls for age, sex and marital status; b-Study control for other factors; c-cohorts are not comparable

*** a-Independent blind assessment; b-record linkage; c-self-report; d-no description; e-other

Supplemental Table 2 Judgement of diagnostic accuracy studies according to QUADAS-2 ⁸

Study	Risk of bias			Applicability concerns			
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ludwin 2019 ¹²⁴	Low	Low	Low	Unclear	Low	Low	Low

Supplemental Table 3 Judgement of the Reliability/agreement studies according to the Quality Appraisal of Diagnostic Reliability (QAREL) ⁷
Study: Ludwin et al. 2019 ¹²⁴

	Yes	No	Unclear	N/A
1- Was the test evaluated in a sample of subjects who were representative of those to whom the authors intended the results to be applied?	X			
2- Was the test performed by raters who were representative of those to whom the authors intended the results to be applied?	X			
3- Were raters blinded to the findings of other raters during the study?	X			
4- Were raters blinded to their own prior findings of the test under evaluation?	X			
5- Were raters blinded to the results of the reference standard for the target disorder (or variable) being evaluated?	X			
6- Were raters blinded to clinical information that was not intended to be provided as part of the testing procedure or study design?		X		
7- Were raters blinded to additional cues that were not part of the test?		X		
8- Was the order of examination varied?		X		
9- Was the time interval between repeated measurements compatible with the (theoretical) stability of the variable being measured?			X	
10- Was the test applied correctly and interpreted appropriately?	X			
11- Were appropriate statistical measures of agreement used?	X			
Total	7			

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Figure 2 Hysterosalpingography of the uterus with two patent tubes. The shape of the uterine cavity can be considered as resembling a "T" instead of a triangle. However, the diagnosis is dependent on subjective judgment and it may be not reproducible between observers. Moreover, the observer cannot be sure whether the uterine cavity is assessed in the coronal or oblique view.

Figure 3 Coronal view of the uterus with curved render modes of 3D TVS (top row: HDlive; Bottom row: Volume Contrast Imaging). The uterine cavity shape can be suspected as being T-shaped based on subjective impression (bottom row), however without measurements the reliability of diagnosis is only moderate among the representative experts. The three sonographic criteria must be present according the CUME group (lateral indentation depth ≥ 7 mm, lateral indentation angle $\leq 130^\circ$ and T-angle $\leq 40^\circ$) for reliable and accurate diagnosis of T-shaped uterus ¹²⁴.

The CUME definition of T-shaped uterus reflect the diagnosis made most often by several representative experts. When the CUME definition and criteria are used, doctors and patients can be confident that the diagnosis of T-shaped uterus has high probability of being correct.

Figure 4 Coronal view of the uterus using three-dimensional ultrasound (a-b), 3D sonohysterography with HDlive render mode (c), and 3D sonohysterography with VCI, and 3D sonohysterography with automatic volume calculation software (SonoAVC; SonoHysteroAVC technique). One of the most important challenges is on how to perform measurements with high reliability considering that subtle uterine contractions and peristalsis can influence the endometrial cavity and the quality of imaging is not perfect. One can consider saline 3D-sonohysterography to

improve the quality of imaging and delineation of the uterine cavity contour. Considering the additional use of automatic volume calculation software¹⁷², it is possible to assess the uterine cavity volume, another interesting parameter for further research, and better understanding the diversity of uterine morphology and its impact on reproductive outcomes .

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants; and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8; 26
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	27-35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	36-41
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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4. Discussão

Mesmo entre observadores bem treinados, o nível de concordância para o diagnóstico do útero em “T” por meio de avaliação subjetiva do corte coronal do útero no estudo CUME foi apenas moderado, e o percentual de concordância foi de 80%. O estudo identificou três medidas com boa precisão e reprodutibilidade de razoável a moderada para o diagnóstico objetivo do útero em formato de “T”: ângulo de endentação lateral ($<130^{\circ}$), profundidade da endentação lateral (>7 mm) e ângulo “T” ($\leq 40^{\circ}$). Na presença dos três critérios, é possível que haja melhor concordância com a opinião mais votada pelos especialistas. Este é o primeiro estudo a propor critérios diagnósticos objetivos e mensuráveis para o útero em “T”.

Os estudos incluídos na revisão sistemática sobre útero em “T” utilizaram diferentes critérios para o diagnóstico desta condição. Além disso, os autores mencionaram diferentes métodos diagnósticos, sendo o US-3D o mais citado. Como as pacientes incluídas nos estudos têm antecedente de infertilidade, abortamento, parto pré-termo, falha de implantação e gravidez ectópica, interroga-se a associação do útero em formato de “T” a desfechos reprodutivos comprometidos. Nos estudos incluídos na revisão, sua prevalência variou de 0,2-10%. As causas relacionadas ao útero em “T” foram sinéquias uterinas, adenomiose, além de ter sido citado como um defeito de causa primária. O tratamento cirúrgico do útero em “T” foi proposto por vários estudos, estando relacionado à melhora importante nos desfechos reprodutivos (taxa de gravidez e de nascido vivo, parto a termo, redução de abortamento e de gravidez ectópica). Entretanto, a qualidade da evidência é muito baixa. Nenhum dos estudos incluiu um grupo controle de pacientes em manejo expectante.

Usar critérios diagnósticos adequados para a definição do útero em “T” é tão importante quanto escolher um método diagnóstico adequado. O estudo CUME contribui para o desenvolvimento de uma linguagem comum no diagnóstico das malformações uterinas, como também auxilia na compreensão e validação da qualidade da evidência sobre o útero em “T”. A definição proposta pelo grupo CUME tem o potencial de facilitar o estudo da prevalência, importância clínica e poderá possibilitar análise dos reais benefícios do tratamento cirúrgico nos desfechos reprodutivos.

É necessário reconhecer se o útero em “T” é realmente uma malformação uterina com consequências clínicas. Até o momento, o seu diagnóstico tem sido subjetivo. O estudo CUME mostrou que, mesmo entre múltiplos especialistas, a concordância do julgamento subjetivo para diagnosticar o útero em “T” não é muito alta, além de ser inviável na prática clínica. Os critérios objetivos propostos pelo estudo CUME poderão ser utilizados em substituição à avaliação por múltiplos especialistas para obtenção de resultados semelhantes, o que proporcionaria melhor acurácia e concordância quando se compara ao julgamento subjetivo de um único especialista, como é feito atualmente na prática clínica.

Variações uterinas sutis, como o útero em forma de “T”, têm sido apontadas como malformações congênitas, e o tratamento cirúrgico tem sido proposto para melhorar a fertilidade (25). Entretanto, não há evidência suficiente para oferecer tratamento cirúrgico na prática clínica, mesmo para mulheres com antecedentes de desfechos reprodutivos prejudicados, como no aborto de repetição (39). O diagnóstico do útero em “T” como anomalia congênita pode ser questionado, podendo ter sido criado por grupos com interesses concorrentes para justificar a indicação de procedimentos cirúrgicos para esta condição (40). A definição proposta pelo ESHRE-ESGE (2) para o útero em “T” não é clara e pode ser mal interpretada, uma vez que o diagnóstico é subjetivo e baseado na impressão do observador. Foi sugerida por especialistas e não foi baseada em evidências científicas (40). Não está claro o que pode ser entendido por cavidade estreita e paredes laterais espessadas por pontos de corte mensuráveis. Por essa definição, não é possível diferenciar o útero em “T” do útero infantil, nem do útero normal. De acordo com a classificação proposta pelo ESHRE-ESGE, aproximadamente 70% das mulheres apresentarão malformação uterina (17). Os relatos de tratamento cirúrgico para o útero em “T” aumentaram muito após essa classificação, que tem sido apontada como potencial fator iatrogênico, promovendo a identificação de malformações em úteros que seriam, na verdade, normais (17,36,38).

O tratamento cirúrgico para o útero em “T” tem revelado os mesmos desafios da conduta para o útero septado. Ressecção histeroscópica para tratamento de septo uterino tem sido realizada há mais de 30 anos a despeito da ausência de evidências de boa qualidade (41,42). A melhor evidência disponível até o momento

sobre o tema provém de uma coorte retrospectiva multicêntrica, que incluiu 257 mulheres ao longo de 37 anos. Nesse período, os métodos diagnósticos utilizados, como também as definições diagnósticas, variaram. Nos primeiros 20 anos do estudo, o manejo expectante foi amplamente empregado em mulheres com septo pequeno, enquanto intervenção foi realizada em pacientes com deformidades maiores. A alocação das pacientes para ressecção do septo ou manejo expectante foi realizada a critério dos especialistas, de forma subjetiva. Atualmente, existe tendência a oferecer tratamento cirúrgico mesmo para mulheres com septos pequenos. No estudo, 80 dentre 151 mulheres submetidas à metroplastia conseguiram pelo menos um nascido vivo (53%), comparadas a 76 dentre 106 mulheres submetidas ao manejo expectante (71,7%) (43), sendo possível concluir que a ressecção uterina não aumenta a taxa de nascido vivo nem diminui taxas de abortamento ou parto pré-termo quando comparada com o manejo expectante. Uma revisão Cochrane (41) não conseguiu identificar ensaios clínicos randomizados que avaliassem o efeito da ressecção histeroscópica do septo nos desfechos reprodutivos. Existe um ensaio clínico randomizado (ECR) recém-concluído, mas ainda não publicado sobre o tema, que levou mais de 10 anos para incluir 68 mulheres (44); a publicação deste estudo trará luz para este tópico, como também para o manejo do útero em “T”, condição em que já se afirma o benefício da intervenção antes de se dispor de evidência de boa qualidade.

Antes de expor mulheres a risco e custos desnecessários, ECRs bem desenhados deveriam investigar a eficácia e segurança de uma intervenção (40). Parece pouco provável que um pequeno aumento na cavidade uterina após incisões de poucos milímetros no fundo/endentações laterais seja relevante, quando se considera o diminuto volume de um embrião e o aumento fisiológico do volume da cavidade uterina durante a gravidez (de 1-3 ml para >4000 ml no final da gestação) (40). Estudos sobre novas intervenções precisam ser lidos com criticidade, uma vez que serão usados como argumento para promover procedimentos que podem ser desnecessários. Há enorme potencial de viés na pesquisa sobre fertilidade, uma vez que tanto a indústria como os pesquisadores estão interessados em provar que as novas técnicas são bem sucedidas (45).

Uma revisão sistemática recente sobre o impacto da metroplastia histeroscópica em mulheres com útero dismórfico com antecedente de abortamento (46) evidenciou que metade das mulheres com histórico de aborto recorrente conseguiu pelo menos um nascido vivo após metroplastia histeroscópica. A classe útero dismórfico (u1), na classificação proposta pelo ESHRE-ESGE (2), inclui dois tipos de útero, além do útero em “T” (u1a): o útero infantil (u1b; cavidade uterina estreita sem paredes laterais espessadas com correlação 1/3 do corpo uterino e 2/3 do colo do útero) e “outros” (u1c; contém todas as deformidades menores da cavidade uterina). Os seis estudos incluídos nesta revisão foram também incluídos na revisão sistemática sobre útero em “T”. Entretanto, os mesmos estudos foram julgados como tendo boa qualidade na revisão de útero dismórfico e baixa qualidade na revisão de útero em “T”. A revisão sistemática sobre útero dismórfico concluiu que o tratamento cirúrgico é efetivo, ao apresentar taxa de nascido vivo de 50%, de gravidez clínica de 73% e de abortamento de 23%. Porém, essas seriam as taxas esperadas sem nenhum tratamento. Ademais, os autores da revisão sobre útero dismórfico realizaram metanálise de estudos retrospectivos sem grupo controle. Os autores enfatizam que não há ECR ou estudos com grupo controle por restrições éticas, e que os resultados por eles encontrados podem indicar a eficácia do tratamento cirúrgico. Entretanto, sem estudos adequados, o real benefício do tratamento do útero em forma de “T” não poderá ser comprovado.

Na revisão sistemática sobre útero em “T”, as implicações clínicas do útero em “T” foram avaliadas em estudos observacionais que utilizaram critérios diagnósticos diversos e mal definidos, além de terem descrito técnicas cirúrgicas diferentes. Não foi possível reconhecer o benefício do tratamento cirúrgico para o útero em “T”, apesar da descrição de melhora importante dos desfechos reprodutivos.

No estudo CUME para o útero em “T”, apesar de ter sido demonstrada concordância moderada no diagnóstico subjetivo entre múltiplos especialistas, a relevância clínica do útero em “T” não relacionado ao DES é desconhecida. As medidas objetivas foram realizadas por observadores muito bem treinados, usando pontos de referência que podem ser difíceis de identificar (como o orifício cervical interno), usando apenas um bloco de US-3D, o que não reflete o que ocorre na

prática clínica, em que há fontes de variabilidade que podem impactar negativamente a acurácia e confiabilidade do diagnóstico. Nesse estudo, foram selecionadas pacientes que apresentavam endentação lateral subjetiva, o que pode ter sido fonte de viés de seleção. Os resultados do estudo não podem ser generalizados para propósito de rastreio ou para úteros com outras malformações.

Para estudos futuros, existe a necessidade de se aplicarem critérios diagnósticos objetivos e mensuráveis para o útero em “T”. As definições propostas pelo estudo CUME poderão auxiliar nisso, além de facilitarem a análise da prevalência do útero em “T” e de sua relevância clínica. Só há, até o momento, estudos que incluíram mulheres com útero em formato de “T” com desfechos reprodutivos prejudicados, e não se sabe, portanto, a relevância desta condição na população geral. Caso estudos futuros confirmem a associação do útero em “T” com desfechos reprodutivos ruins, ensaios clínicos randomizados com grupo controle de pacientes em manejo expectante devem ser realizados para avaliar os benefícios da metroplastia histeroscópica nos resultados reprodutivos. Até o momento, não há evidências suficientes para apontar o útero em “T” como uma malformação uterina, mas como uma variante do útero normal, a fim de evitar intervenções desnecessárias sem que haja comprovação dos reais benefícios.

5. Conclusões

A concordância entre múltiplos especialistas é apenas moderada para o diagnóstico do útero em “T”. Três medidas com boa acurácia diagnóstica e razoável a moderada confiabilidade foram propostas para o útero em “T”: profundidade da endentaço lateral ≥ 7 mm, ngulo de endentaço lateral $\leq 130^\circ$ e ngulo “T” $\leq 40^\circ$. At o momento, no se sabe a prevalncia, as possveis etiologias e a relevncia clnica do tero em “T”, uma vez que os estudos disponveis no utilizaram critrios diagnsticos objetivos para a anlise dessa condio. Pouco se sabe sobre os benefcios da metroplastia histeroscpica no tratamento do tero em “T”, uma vez que no h ensaios clnicos randomizados que incluam grupo controle. A definio proposta pelo grupo CUME para o tero em “T”, baseada em critrios objetivos mensurveis, poder auxiliar no desenvolvimento de estudos futuros sobre o tero em formato de “T”.

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7. Anexos

ANEXO A - AUTORIZAÇÃO DA REVISTA PARA PUBLICAÇÃO DO ARTIGO “Congenital Uterine Malformation by Experts (CUME): T-shaped uterus”

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ANEXO B - COMPROVANTE DE SUBMISSÃO DO ARTIGO “Definitions, prevalence, clinical implications and treatment of t-shaped uterus: systematic review”

30-Apr-2020

Manuscript number: UOG-2020-0491

Dear Dr Coelho Neto

We are pleased to receive your manuscript entitled Definitions, prevalence, clinical implications and treatment of T-shaped uterus: systematic review by Coelho Neto, Marcela; Ludwin, Artur; Petraglia, Felice; Martins, Wellington. We will shortly be assigning it to one of the Journal's Editors who will handle the peer review of the paper.

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Please remember in any future correspondence regarding this article to always include its manuscript ID number UOG-2020-0491.

Many thanks for submitting your manuscript

Yours sincerely

Sarah Hatcher
Managing Editor

ANEXO C - DISPENSA DE ANÁLISE PELO CEP

Ribeirão Preto, 15/10/2018

À coordenação do Comitê de Ética em Pesquisa do HCRP e FRMP - USP

Cara Professora Dra. Márcia Guimarães Villanova,

Venho, através desta, solicitar dispensa de análise pelo Comitê de Ética em Pesquisa para o projeto intitulado "Congenital Uterine Malformations by Experts (CUME): what is T-shaped uterus?" (Malformações congênitas do útero por especialistas – (CUME): o que é útero em "T"?), a ser desenvolvido no Departamento de Ginecologia e Obstetrícia (DGO) do HCRP. A pesquisadora responsável pelo estudo é Marcela de Alencar Coelho Neto, aluna de doutorado do DGO. O orientador do estudo é o professor Wellington de Paula Martins.

O estudo foi aprovado pelo DGO, mas foi solicitado que o mesmo deve ser enviado ao Comitê de Ética em Pesquisa do Hospital das Clínicas de Ribeirão Preto para análise, antes do início de sua execução.

O estudo em questão se trata de um estudo em conjunto com outra instituição (Universidade Jagiellonian, Cracóvia, Polônia), cujo comitê de ética já aprovou sua realização. O pesquisador participante da referida instituição se chama Artur Ludwin (citado no projeto de pesquisa como pesquisador envolvido).

Estamos fazendo tal solicitação porque os pesquisadores brasileiros não terão contato com as pacientes do estudo, nem com prontuários. A pesquisa será realizada através da análise de blocos de ultrassonografia 3D anônimos, previamente colhidos e armazenados pelos pesquisadores da Polônia e enviados para os pesquisadores brasileiros via nuvem (arquivos salvos no Dropbox). Todas as pacientes do estudo são da Polônia e assinaram termo de consentimento para participarem do estudo.

A realização do estudo não implicará em custos para a Faculdade de Medicina de Ribeirão Preto, uma vez que os exames de ultrassonografia foram realizados em outra instituição, e os dados serão analisados nos computadores dos próprios pesquisadores. A análise estatística e redação do estudo também serão realizadas pelos autores do estudo. Não será solicitado nenhum financiamento para sua execução.

Atenciosamente,

Marcela de Alencar Coelho Neto

Não há necessidade de submissão ao
Comitê de Ética em Pesquisa:
Marcelina Villanova
Dra. Márcia Guimarães Villanova
Coordenadora do Comitê de Ética em Pesquisa
do HC e FRMP-USP
22/10/18

Marcela de Alencar Coelho Neto

Aluna de doutorado do DGO

A handwritten signature in black ink, reading "Wellington de Paula Martins". The signature is written in a cursive, flowing style.

Wellington de Paula Martins

Orientador

UNIVERSIDADE DE SÃO PAULO**FACULDADE DE MEDICINA DE RIBEIRÃO PRETO****PROJETO DE PESQUISA**

Malformações congênitas do útero por especialistas (Congenital Uterine Malformation by Experts-CUME):
o que é útero em “T”?

LINHA DE PESQUISA

Mecanismos envolvidos na foliculogênese e determinantes da qualidade oocitária/embrionária e da interação gamética, o ambiente intrafolicular e endometrial relacionados à fertilidade.

NUCLEO DE PESQUISA ou SETOR

Setor de Reprodução Humana do Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de
Ribeirão Preto, USP, Ribeirão Preto, SP.

LOCAL DE EXECUÇÃO

Setor de Reprodução Humana do Hospital das Clínicas da FMRP-USP, Ribeirão Preto, São Paulo.

Jagiellonian University, Krakow, Poland.

PESQUISADOR RESPONSÁVEL

Wellington P. Martins

PESQUISADORES ENVOLVIDOS

Marcela A. C. Neto; Artur Ludwin; Wellington P. Martins.

PERIÓDICO-ALVO**QUALIS**

Fertility and Sterility

A1

Ultrasound in Obstetrics and Gynecology

A1

Ribeirão Preto 2018**Abstract**

Introduction: T-shaped uterus is a uterine malformation characterizes by the presence of lateral indentation, with a severe narrowing of the uterine cavity from the lateral sides, what makes the shaped of the endometrial cavity resembles a “T” instead of a triangle. T-shaped uterus is commonly related to in uterus exposure to Diethylstilbestrol (DES), a medication using until 1980’s to prevent miscarriage, but it can also be related to Asherman syndrome or pelvic tuberculosis besides the possibility of having no etiology identified. There is no consensus on the gold standard ultrasound technique for diagnosing T-shaped uteri and no strict parameters for its definition.

Objective: This study aims to analyze previously recorded 3D ultrasound datasets containing images from the uterus subjectively classified as being T-shaped uterus or not by experts, to develop possible measurements that may be used to establish objective diagnostic criteria for T-shaped uterus considering reproducibility and accuracy of the measurements between observers.

Methods: Observational prospective study to evaluate reproducibility, agreement, diagnostic accuracy and elaboration of an algorithm to differentiate T-shaped uterus from normal uterus. The patients of the study will be evaluated in the Jagiellonian University, Krakow, Poland. The 3D-US datasets will be sent to the other researchers. To achieve a consensus in differentiating T-shaped uterus from normal uterus, images originated from 3D-datasets will be sent to fifteen experts in the field of ultrasound, gynecology and gynecologic surgeries who will perform subjective judgements (each patient will be classified as having T-shaped uterus or normal uterus). Two expert observers (WPM and AL) will perform some measurements in the uteri, using 3D datasets previously recorded, to draw an algorithm to diagnose T-shaped uterus. Then, the reproducibility and the accuracy of these measurements will be estimated by CCC. The agreement between

the two observers regarding the measurements made will be evaluated by Cohen's kappa and weighted Cohen's Kappa.

Key words: Mullerian ducts, Congenital Uterine Anomalies, T-shaped uterus, Dysmorphic uterus Agreement

Resumo

Introdução: Útero em “T” é uma malformação uterina caracterizada pela presença de endentação lateral, com um severo estreitamento da cavidade uterina nas laterais, o que faz o formato da cavidade endometrial lembrar um “T” em vez de um triângulo. Útero em “T” é comumente associado à exposição ao dietilestilbestrol (DES), uma medicação usada até a década de 80 para prevenir abortamento, mas também pode estar relacionado à síndrome de Asherman ou à tuberculose pélvica, além da possibilidade de não ter etiologia identificada. Não existe consenso em relação à técnica padrão-ouro para diagnóstico do útero em “T” e nem parâmetros estritos para sua definição.

Objetivo: Este estudo tem como objetivo analisar blocos de dados de ultrassonografia 3D (US-3D) previamente gravados contendo imagens de úteros subjetivamente classificados como sendo útero em “T” ou não por especialistas, a fim de desenvolver possíveis medidas que possam ser usadas para estabelecer critérios diagnósticos objetivos para útero em “T” considerando a reprodutibilidade e acurácia das medidas entre observadores.

Métodos: Estudo prospectivo observacional para avaliar reprodutibilidade, concordância, acurácia diagnóstica e elaboração de um algoritmo para diferenciar útero em “T” de útero normal. As pacientes do estudo serão avaliadas na Universidade Jagiellonian, na Cracóvia, Polônia. Os blocos de dados de US-3D serão enviados para os outros pesquisadores. Para alcançar um consenso em diferenciar útero em “T” de útero normal, imagens oriundas dos blocos de US-3D serão enviadas para quinze especialistas no campo da ultrassonografia, ginecologia, cirurgia ginecológica, que irão julgá-las subjetivamente (cada paciente será classificada como tendo útero em “T” ou útero normal). Dois especialistas irão realizar algumas medidas no útero, usando os blocos de US-3D previamente gravados, para desenvolver um algoritmo para diagnosticar útero em “T”. A seguir, a reprodutibilidade e acurácia destas medidas será estimada pelo CC (coeficiente de correlação de concordância). A concordância entre os dois observadores em relação às medidas feitas será avaliada pelo Cohen kappa e pelo Cohen kappa ponderado.

Key words: ductos Mullerianos, Malformações uterinas congênitas, útero em “T”, concordância do útero dismórfico.