

**INFERTILITY AND T-SHAPED UTERUS WITHOUT DIETHYLSTILBESTROL (DES)
EXPOSURE: A CASE REPORT AND LITERATURE REVIEW****Richard Ngendabanyikwa*, Amal Benbella, Nouhaila Haoussani, Zakia Tazi, Abdelhay Adib Filali, Mohamed Hassan Alami, Rachid Bezad.**

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ABSTRACT

Despite the frequency of uterine abnormalities in infertile women (40% to 50%), infertility of exclusively uterine origin represents only 2 to 3% of infertility. This is due to the frequent association of uterine lesions with other causes of infertility. These lesions can interfere with spontaneous fertility or affect the results of medically assisted procreation (MAP). 3D ultrasound and MRI are currently the techniques that have demonstrated the best results in terms of sensitivity and specificity. A Metroplasty is a surgical intervention which aim to restore normal uterine anatomy in certain uterine malformations, with a goal to improve the obstetrical prognosis. Enlargement metroplasty certainly has a positive impact on the outcome of reproduction in patients with uterine hypotrophy and/or dysmorphism, particularly in women who have been exposed to Diethylstilbestrol (DES) in utero. However, there is a lack of Evidence to offer this intervention as a first-line therapy, apart from specific cases such as elderly nulligest or before inclusion in medically assisted procreation (AMP).

KEYWORDS: Infertility, uterine malformation, 3D ultrasound, T-shaped uterus, Metroplasty.**I. INTRODUCTION**

Despite the frequency of uterine abnormalities in infertile women (40% to 50%), infertility of exclusively uterine origin represents only 2 to 3% of infertility. This is due to the frequent association of uterine lesions with other causes of infertility. These lesions can interfere with spontaneous fertility or affect the results of medically assisted procreation (MAP). Through uterine cavity, the sperm can travel to encounter the ovule (female gamete) in fallopian tube so that fertilization can occur.^[5] It is also the site of implantation and development of the fertilized egg.^[5,10] Several pathological processes can interfere with these This Physiological Phenomenon and lead to infertility, these lesions may be submucosal or interstitial myomas, polyps, synechies, uterine septate or uterine hypotrophy and/or dysmorphism... etc.^[3,10]

A septate uterus is the most common uterine malformation. Its prevalence is estimated at 1% in the female population.^[1,2] This rate is stable for both fertile and infertile women, and is expected to increase to 3.3% for women with repeated miscarriages.^[1,5] A septate uterus are generally considered to have the worst obstetric prognosis with a live birth rate between 6% and 28% and a high rate of spontaneous abortion above 60%.^[1,5] However, there is very little literature on the impact of untreated müllerian malformations on fertility.

Only one retrospective study was found where the uterus was evaluated by hystereography and coelioscopy or laparotomy in over 3000 patients.^[1,2] In this study, the frequency of uterine malformations was 4% (1). Also was more common in infertile women than in sterile women (6.3 vs 2.3%).^[1,4] One-third of the malformations (33.6%)^[1,4] were in utero compartments. In the case of uterine septum, the rate of early spontaneous abortions was 25.5%, late abortions was 6.2%, premature deliveries was 14.5%, full-term deliveries was 51.7%, and the live birth rate was 62%. Therefore, the obstetric prognosis was better than expected, even if it was lower than that of the general population.^[1] The Arcuate uterus had no impact on obstetric prognosis, which is commonly accepted by all authors.^[1,4]

The mechanisms to explain the fetal losses in uterine septe are not well clear likely due to poor vascularization of the septate and endometrium, high pressure intrauterine, cervical insufficiency, disorders of myometrium contractility, myometrium and/or endometrial hormone receptor deficiency.^[1,4]

Metroplasties are surgical procedures that aim to restore normal uterine anatomy in some uterine malformations, in order to improve the obstetrical prognosis. Enlargement metroplasty certainly has a positive impact on the outcome of reproduction in patients with uterine

hypotrophy and/or dysmorphism, particularly in women who have been exposed in utero to Diethylstilbestrol (DES). However, there is a lack of Evidence to offer this intervention as a first-line therapy, apart from specific cases such as elderly nulligest or before inclusion in medically assisted procreation (AMP). In women with

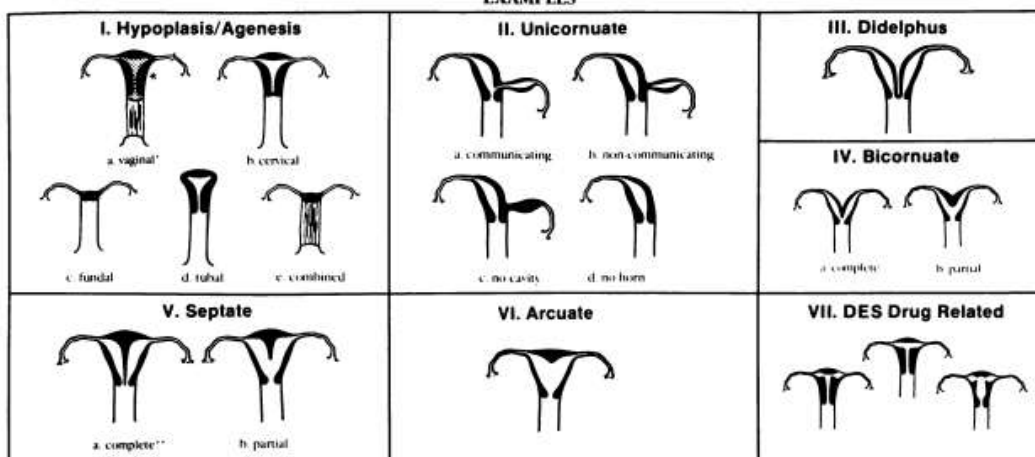
repeated miscarriages, metroplasty appears to significantly improve the prognosis of pregnancies.

Several studies have already reported cases of T- shaped uterus to patients who were exposed to diethylstilbestrol (DES).

The aim of this study is to report the case of a T-shaped uterus with no evidence of diethylstilbestrol (DES) exposure in a patient undergoing infertility treatment. Another particularity of this observation is that three-dimensional ultrasonography, complemented by diagnostic hysteroscopy, revealed the uterine malformation that had gone unnoticed on 2D ultrasonography, enabling the diagnosis and therapeutic indication to be established.

Classification des anomalies du tractus génital féminin par l'ESHRE (The European Society of Human Reproduction and Embryology) et ESGE (European Society for Gynaecological Endoscopy) - 2013			
Utérus	Classes principales	Sub-classes	
U0	Utérus normal		Dans l'utérus normal, l'indentation (échancre ou la saillie) utéro-fundique médiane n'excède pas le taux de 50% de l'épaisseur de la paroi utérine (en nombre absolu < 5 mm).
U1	Utérus dysmorphique	U1a : Utérus en T	L'utérus en "T" se caractérise par une cavité utérine étroite, en forme de T due à l'épaisseur exagérée des parois utérines latérales. Le corps utérin occupe les 2/3 de la longueur de l'utérus et le col utérin (cervix) occupe le 1/3 de cette longueur.
		U1b : Utérus infantile	L'utérus infantile se caractérise par une cavité utérine étroite sans épaissement des parois latérales et un rapport inversé entre la longueur du corps de l'utérus (le 1/3) et le col de l'utérus (2/3).
		U1c : Autres	Y compris les utérus avec une indentation intérieure (un éperon ou une saillie) au niveau fundique médiane < à 50 % de l'épaisseur de paroi utérine. Habituellement, les utérus dysmorphiques sont plus petits en taille comparés aux utérus normaux.
U2	Utérus cloisonné (septate uterus)	U2a : partiel U2b : complet	Utérus extérieurement normal avec une indentation (une éperon ou une saillie ou un septum) fundique interne médiane supérieure à 50 % de l'épaisseur de la paroi utérine. Cette indentation est sous forme de septum divisant partiellement (U2a) ou complètement (U2b) la cavité utérine et parfois le col utérin (U2b/C1) et/ou le vagin (= et/ou V1 ou V2).
U3	Utérus bicorporeal (bicorporeal uterus) (alias = utérus bicorné)	U3a : partiel U3b : complet U3c : utérus bicorporeal cloisonné (bicorporeal septate uterus)	Il s'agit d'une anomalie utérine fundique extérieure : l'indentation fundique extérieure (le sillon ou la fissure ou la scissure) médiane excède le taux de 50% de l'épaisseur de la paroi utérine ; cette indentation anormale peut être partielle (U3a), ne concerne que le corps de l'utérus, ou complète (U3b) incluant le corps et col de l'utérus (U3b/C2) et/ou le vagin (et/ou V1 ou V2). L'utérus bicorporeal cloisonné U3c se caractérise l'épaisseur l'indentation fundique médiane qui est supérieure à 150 % de l'épaisseur de paroi utérine.
U4	Hémi-utérus (hemi-uterus) (alias = utérus unicorne)	U4a = hémi-utérus avec la présence d'une cavité controlatérale rudimentaire communiquant ou non à cette hémi-utérus U4b = hémi-utérus sans la présence d'une cavité controlatérale rudimentaire (corne controlatérale sans cavité ou absence de corne controlatérale).	

AMERICAN FERTILITY SOCIETY CLASSIFICATION OF MULLERIAN ANOMALIES



* Uterus may be normal or take a variety of abnormal forms.
 ** May have two distinct cervixes

II. OBSERVATION

Mrs D Z K, 31 years old, married for 13 years, nulligeste nullipare. The patient has been followed for infertility, her history is marked by the presence of irregular cycles and spaniomenorrhea, no contraception methods is used. She had a tubal plasty surgery by coelioscopy in 2016. during the operation, the pelvis was adherent, with bilateral tubal phimosis. Despite the adhesions lysis and salpingoplasty, the blue test was negative at the end of the procedure. A hysteroscopy coupled with coelioscopy had made in succesful to lyse cervical synechias. The exploration of the uterine cavity by hysteroscopy had not proven any abnormalities. Due to the failure of the tubal plasty, the patient was referred to us for medical assisted reproduction management. On general examination, the blood pressure was 12/7 cmHg, body mass index (BMI) 23kg/m². On speculum examination, the cervix and vaginal walls with normal appearance, the uterus with normal size, mobile without any palpable adnexal mass. The rest of the somatic examination was without particularity.

The hormonal tests were ordered; the AMH (Antimüllienian Hormone) = 6.23 ng/ml (normal), TSH (Thyroid Stimulating Hormone) = 1.39 mUI/L (normal) and prolactinemia at 15.34 ng/ml (normal).

The 2D pelvic ultrasound was performed on the 3rd day of the cycle objective a uterus of normal size, homogeneous echostructure, with regular contours, also a thin and regular endometrium of 2.2mm, the ovaries were in normal size with a follicular count of 24(**Fig1**). The husband's spermogram was normal with a volume = 3.8ml, a pH = 8, a concentration = 115.06 Million/ml, a number = 437.228 Million/ejaculate, with a mobility =79% and unmobility at 3%, morphology was at 16%. Serologies of hepatitis B, hepatitis C, HIV (human

immunodeficiency virus) and syphilis in both the patient and her husband were negative.

Because of bilateral tubal obstruction, in vitro fertilization (IVF) was conducted in antagonistic protocol with 200 IU of gonadotropin (GONAL F) from the 2nd day of the cycle and 0.25mg of Cetrorelilix (Cettrotide) from the 6th day of stimulation. A 250µg injection of choriogonadotropin could triggered and 17oocytes were collected. After fertilization, 16 oocytes were fertilized. However, to prevent ovarian hyperstimulation syndrome, all embryos were vitrified or 12 embryos on Day 3 post insemination. During ovarian stimulation, we noted that despite the high levels of estradiol (4089 pg/ml on the day of stimulation, the thickness of the endometrium remained less than 7mm. A The three-dimensional pelvic ultrasound was therefore performed, shoven a normal sized uterus, homogeneous ultrasound structure, regular contours with thickening of the walls, and a thin endometrium with T image of the uterine cavity(**Fig 2**). As a result, a diagnostic hysteroscopy was done, which confirmed the tubular appearance of the uterine cavity. The surgical gesture was carried out at the same time by hysteroscopy, using a 9 mm resector with hook and a knife electrode allowing the resection of a fundal septum of about 1cm, and the reduction of the lateral uterine walls by about 8 mm until the Tubal ostium membranes can be visualized. Six weeks after the enlargement metroplasty, a diagnostic control hysteroscopy objectived a normal size uterine cavity. And the patient benefited from a transfer of frozen embryos.

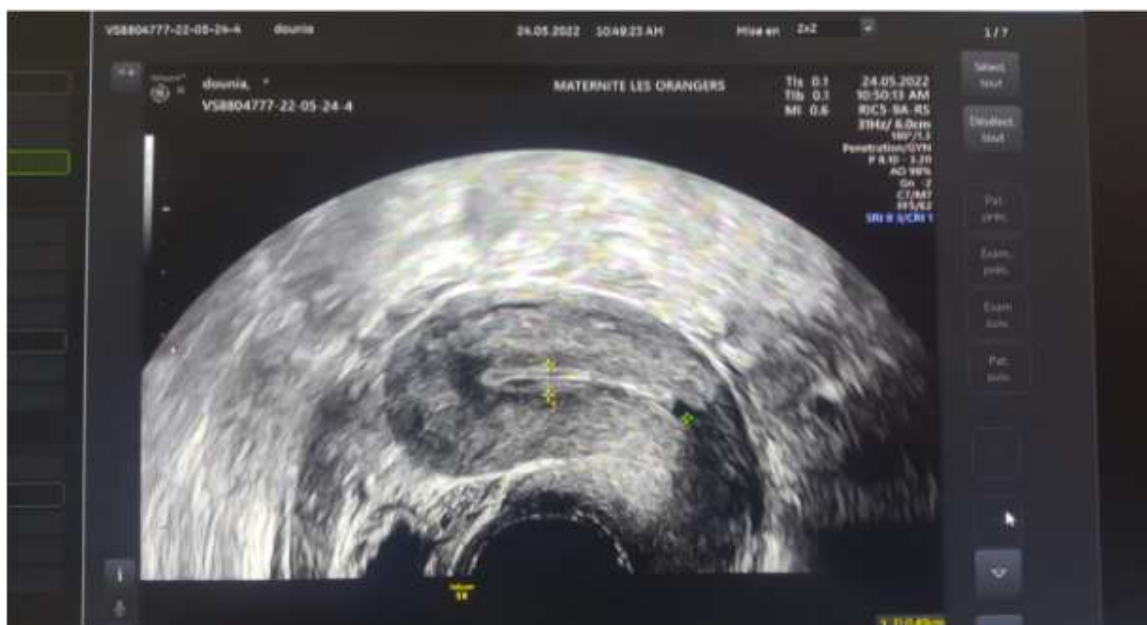


Fig. 1: The two-Dimensional Pelvic Ultrasound, Sagittal Section of The Uterus Without Abnormalities.



Fig. 2: Three Dimensions Pelvic Ultrasound: Reconstruction of The Uterus In, Frontal Section Showing Thickening of The Lateral Walls And A Fundal Partition, Realizing A T-Shaped Uterus.

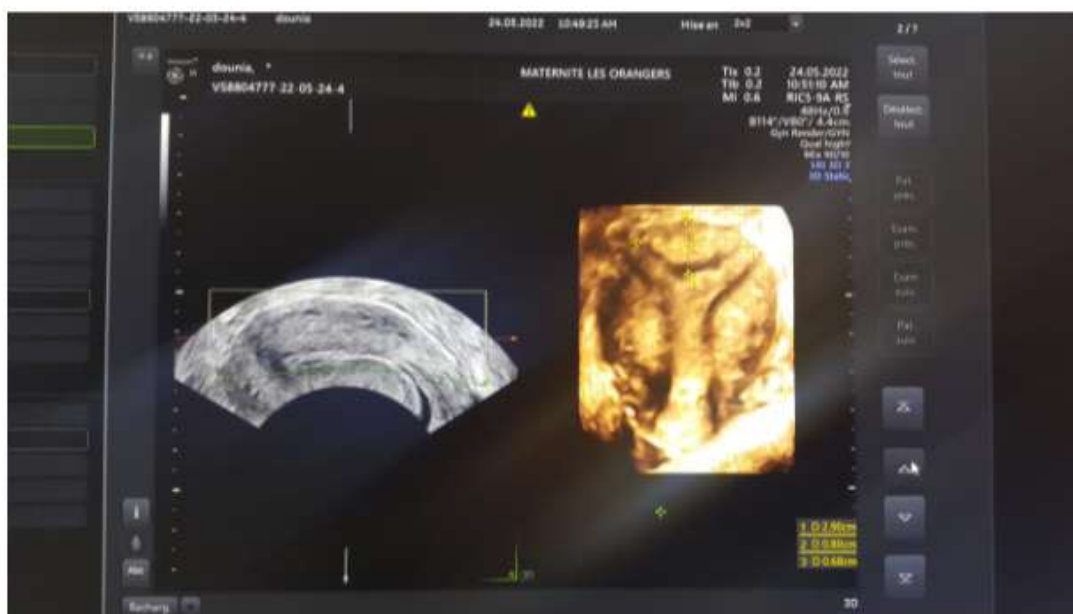


Fig. 3: Comparison between images of a 2D and 3D uterine ultrasound.

III.DISCUSSION

T-shaped uterus (hypoplasia of the uterus), a rare malformation and has mainly been described in patients who experienced intrauterine exposure to diethylstilbestrol in France up until 1977.^[2,5] This malformation falls into ESHRE category type U1.^[7] We must differentiate between harmonious hypoplasias of the uterus, or *uterus infantilis*, linked to hypoestrogenism and frequently associated with primary amenorrhea) and T-shaped hypoplasias, since the harmonious type should not be considered for surgery under any circumstances.^[6,9] The classic imaging methods to assess uterine Malformations are 2D ultrasound and hysterosalpingography. New diagnostic criteria have

been developed with the advanced new diagnostic imaging methods (3D ultrasound, hysterosonography, pelvic MRI).^[4,12] The 3D ultrasound and MRI are currently the best techniques in terms of sensitivity and specificity.^[6,7] It is important to complete with renal imaging to visualize any associated urinary tract malformations which are very common.

Ultrasound enable to evaluate the uterine biometrics (length less than 70 mm, distance between intercornual lines less than 40 mm) and to measure the thickness of the lateral walls of the myometrium. The three-dimensional ultrasound provides an overview of the endometrial-myometrium on coronal plane, measurement

of the subcorneal thickness of the myometrium, and evaluation of any possible endoscopic hysteroplasty is needed.^[10-11] The three-dimensional reconstruction of the frontal plane makes it very easy to obtain an anatomical image of the malformation and often helps to distinguish between the bicornuate uterus and the septate uterus. Also guide the endoscopic resection of the septum by giving the operator a precise idea of its morphology, and height in particular.^[10-11]

The uterine analysis performed mainly on the coronal section of the uterus must include 3 sets of differentiation criteria:

- The analysis of the morphology of the uterine fundus and serous next to: if **Fundal internal indentation** is present and greater than 10 mm, the uterus is most likely bicornuate; if the **external contour** is convex or flat, the uterus is most likely septate, regardless of the appearance of the cavity (which seems to be a less reliable criteria); there are cases of septate uterus where the incision is present but if it less than 10 mm, the diagnosis remains that of a septate uterus.^[7,12]
- The analysis of the uterine cavity (shape, contours, etc.) and the inter-cavity septum.

Another diagnostic tool, used in hysteroscopy and then ultrasound is the sign of the interostial line, the line joining the two ostia on a coronal section of uterus. If it is less than 4 cm, the uterus is septate.^[5,7]

In our case, the 2D ultrasound was first performed and shown a uterus without abnormalities with a cavity without particularity, and the endometrium thickness was 4.9mm. Afterwards the 3D ultrasound was realized and revealed a septum of 8.6mm and lateral uterine walls thickness of 6mm, an interostial distance of 2.86cm, making a T-shaped uterus. Septate uterus are the most common uterine malformations with the poor obstetric prognosis. According to the height of a septum, different types are noted: complete septate uterus, Partial septate uterus and rare, asymmetric septate.

Our patient had a partial uterus septate. The infertility is not systematic. A hysteroplasty should be discussed in the presence of a uterine septate. Two anatomical types, which hysteroplasty is not indicated: complete septate uterus (good prognosis, except in case of marked hypoplasia of both cavities) due to high risk of cervical insufficiency due to surgery, and arcuate uterus that has no negative obstetric impact.^[3]

In utero exposure to DES is often responsible for uterine dysmorphisms. The most pejorative forms are T-shaped uterus, hypoplastic cavity, medio-cavitary stricture. These iatrogenic abnormalities often resemble hypoplastic malformations where there is some degree of bifidity (described as a three-pointed star). Overall are due to an underdevelopment of Müllerian ducts, characterized by uterine length less than 70 mm,

intercorneate distance less than 40 mm, cavity volume less than 3 cm³.

In general, we can distinguish harmonious and disharmonious hypoplasia (uterus in Y or T). Diethylstilbestrol (Distilbene®) exposure in utero is currently the main source.

In our case, the patient without notion of exposure to DES, presents with uterine lateral walls thickness, associated with a T shaped uterus as shown on the three-dimension ultrasound images. The uterine length was 60,2mm, the intercorneate length was at 28.6mm. These abnormalities have poor obstetrical prognosis, and could not benefit from any effective treatment. In our case, a hysteroplasty was performed to enlarge the lateral walls, and to remove the uterine septum.

The metroplasty should not be indicated systematically as a first choice in the absence of infertility and/or pregnancy accident, but it seems justified propose this intervention in case of repeated abortions or repeated failures of assisted reproductive technologies.^[4,5] In our case it was a 13-year-old case of infertility with bilateral tubal obstruction and candidate for in vitro fertilization.

IV. CONCLUSION

A uterine malformations (MU) are congenital malformations of female reproductive system during embryogenesis. The incidence of uterine malformations is difficult to assess in the literature; it is estimated between 1 and 10% in the general population. In infertile women, the frequency of Uterine Malformations is between 3 and 3.5%. They can manifest as gynecological disorders or have an impact on reproduction. Every clinician should look for an uterovaginal malformation in the presence of primary amenorrhea, abdominal pain, repeated miscarriages and in some adverse obstetric outcomes.

2D Ultrasound is not sufficient to visualize these intra-uterine malformations. Their diagnosis and prognostic evaluation require a specific assessment (3D ultrasound, hystereosonography, MRI). Hysteroscopic treatment of the septate uterus appears to be beneficial.

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