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# MULLERIAN DUCT ANOMALIES AND INFERTILITY

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Abstract: Female genital tract congenital anomalies constitute a large group of malformations. Several classifications have been proposed in the past, notably the Musset classification in the French-speaking world, or the AFS classification in the English-speaking world. However, a unification of language has been essential for an accurate diagnosis and a codified and optimal management, this was the objective of the ESHRE/ESGE classification proposed in 2013 classifying female genital tract malformations into uterine (U0 to U6), cervical (C0 to C4) and vaginal (V0 to V4) anomalies. (2) The prevalence of these malformations is often difficult to calculate because of the heterogeneity of the population studied, the divergence of clinical expressions, the multitude of diagnostic tools, and also the different classifications used. However, studies have been done to calculate the prevalence of uterine malformations in the general population and in different subpopulations (infertile women, recurrent miscarriages, etc.). In Morocco, there is no actual study calculating the prevalence in the general population. The clinic is often not very helpful in the diagnosis of uterine malformations, hence the interest in efficient, reliable and least invasive diagnostic tools, which requires the development of hysterosonography in our institutions, as well as 3D ultrasound and MRI, before moving on to hysteroscopy/laparoscopy, which has a diagnostic but above all therapeutic role. The treatment of genital malformations depends essentially on the type of malformation. The bicornuate uterus does not require surgical intervention, in contrast to the septate uterus and cases of vaginal diaphragms, where surgical intervention significantly improves fertility. In our work, the impact on fertility of the treatment of genital tract anomalies has been studied.

#### Introduction:

Infertility is defined by the World Health Organization (WHO) as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (26). Among the etiologies of female infertility, we note malformations of the female genital tract, which is defined as a congenital malformation resulting from a defect or an arrest in the development of the female reproductive system during embryogenesis.

The aim of this study is to establish the epidemiological profile of women with primary or secondary infertility associated with female genital anomalies, to assess the contribution of the different complementary examinations in the diagnosis of genital tract malformations, but above all to evaluate the impact of treatment of these malformations on fertility.

## Materials and methods:

This work reports the results of a retrospective study on 18 patients followed and treated for primary or secondary infertility associated with a genital tract malformation.

This study was conducted in the department of gynecology-obstetrics I, at the Mother and Child Hospital of the University Hospital Hassan II Fez, from January 1, 2015 to June 1, 2019, i.e. a period of 54 months.

The aim of the study is to establish the epidemiological profile of women with primary or secondary infertility associated with a female genital anomaly, but also to evaluate the contribution of the different complementary examinations in the diagnosis of utero-vaginal malformations. Then, our work will evaluate the impact of the treatment of utero-vaginal malformation on fertility, to finally compare the results obtained with those of the literature.

#### **Results:**

18 cases of women with female genital tract congenital anomalies out of a population of 90 women who present primary, secondary infertility i.e., percentage of 20%. The mean age was 30.16 +/-5.18 years, with extremes of age ranging from 22 to 42 years. 09 patients had primary infertility (50%), of which 05 had a septate uterus, 01 had a dysmorphic uterus and 03 had a vaginal anomaly. 09 patients had secondary infertility (50%) of which 08 had a septate uterus and 01 had a bicorporeal uterus. The clinical examination is not very helpful in the case of uterine anomalies, unlike vaginal anomalies. The paraclinical examinations used are 2D ultrasound, hysterosalpingography, MRI, diagnostic hysteroscopy, and diagnostic laparoscopy. The sensitivity of 2D ultrasound was 80% in our series. Hysterosalpingography has a sensitivity of 88.8% in the diagnosis of uterine malformations, however it remains a poor examination in the precise diagnosis of the different types of Müllerian duct anomalies with an error

rate of 22.2%. MRI has a sensitivity of 100% in our series. The diagnosis of certitude is made by diagnostic hysteroscopy associated with diagnostic laparoscopy; this combination of hysteroscopy and laparoscopy was performed in 46.6% of cases. The therapeutic management depends on the type of uterine anomalies, a hysteroscopic resection of the uterine septum is performed in the case of a septate uterus. The patient with a T-shaped dysmorphic uterus will benefit from an enlargement hysteroplasty. Therapeutic abstention is the rule in the case of a bicorporeal uterus. The evolution was as follows: 100% of women with vaginal anomaly were able to carry a pregnancy to term after treatment. 38.4% of the women with a septate uterus were able to carry a pregnancy to term after treatment.

No intraoperative or postoperative complications were noted in the patients of our series.

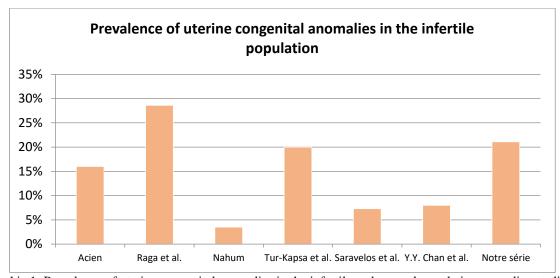
#### **DISCUSSION:**

## I. Epidemiological aspect:

It is difficult to assess the real incidence and prevalence of female genital tract congenital anomalies, whether in the general population, infertile or with a history of premature deliveries or recurrent miscarriages. This difficulty is due to numerous methodological biases related to the large heterogeneity of the populations studied, the types of studies (prospective or retrospective), the diagnostic methods and the classifications used.

According to Saravelos et al (4), the prevalence of congenital uterine anomalies in the fertile/general population is 6.7%. According to Raga et al (1) the prevalence of uterine anomalies in the general population is 3.8% compared to 28.6% in the infertile population. According to Nahum's study (3) uterine malformations were identified in 1 out of 594 fertile women (0.17%) and in 1 out of 29 infertile women (3.5%). This difference was statistically significant. According to the study by Y.Y. Chan (25) the prevalence of septate uterus is increased in women with a history of miscarriage and those who have combined infertility and miscarriage. The role of uterine malformations in infertility is still unclear. However, it has been suggested that uterine anomalies may contribute to infertility, by possibly interfering with normal implantation and placentation (Taylor and Gomel, 2008 (5)). In the Saravelos study, a sub-analysis clearly shows an increased prevalence of septate uterus in the infertile population compared to the general/fertile population: 1.1 to 3.9%. This increase in the prevalence of septate uterus in the infertile population clearly demonstrates a link between these two entities.

In our series:



Graphic 1: Prevalence of uterine congenital anomalies in the infertile and general population according to different studies.

In our study, the prevalence of female genital tract anomalies in the infertile population is 20%, which is close to the results of the studies of Raga et al, Acien and Tukaspa. The diagnostic methods used in our series are optimal.

#### II. Paraclinical examinations:

1) Biological investigation of infertility:

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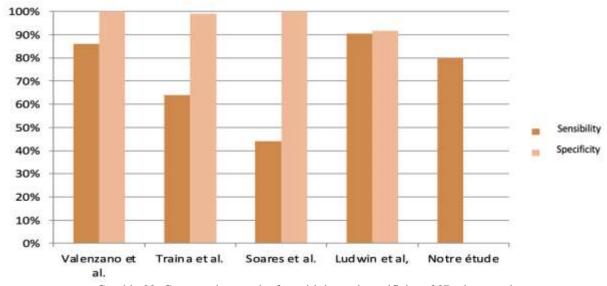
A workup in the context of infertility was requested in all our patients, including the dosage of FSH, LH, estradiol, prolactinemia, TSH and the spermogram of the husband. All these investigations came back normal in all our patients.

# 2) Radiological investigation

The different imaging methods used in the assessment of uterine anomalies are 2D or 3D ultrasound, hysterosonography, hysterosalpingography and MRI. These different techniques may be combined and, depending on the type of malformation, may be complementary.

## a. 2D/3D pelvic ultrasound:

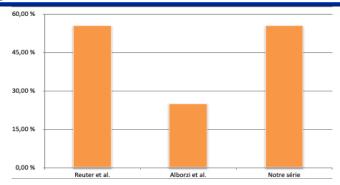
Transabdominal or transvaginal ultrasound is an accessible diagnostic tool. Vaginal ultrasound is the first-line examination; the 3D mode is particularly useful in this indication. In the study by Traina E et al. 2D ultrasound demonstrated a sensitivity of 64% and a specificity of 99% (28). In the study by Soares et al. 2D ultrasound demonstrated a sensitivity of 44% and a specificity of 100% (29). In a prospective study of 117 patients made by Ludwin in 2013, 3D transvaginal ultrasound had a sensitivity of 97.1% and a specificity of 100% (97.4%), 2D transvaginal ultrasound (performed by an expert) had a sensitivity of 90.5% and a specificity of 91.7%. In the Ludwin and Moini studies, 3D ultrasound alone was found to be 88% accurate in diagnosing septate uterus compared with hysteroscopy/laparoscopy (6,7). In our series, the sensitivity of ultrasound in our series is 80% which is concordant with the data in the literature.



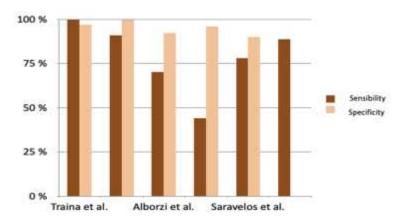
Graphic 02: Comparative graph of sensitivity and specificity of 2D ultrasound

## b. Hysterosalpingography (HSG):

Hysterosalpingography does not evaluate the external shape of the uterus and therefore cannot reliably differentiate a septate uterus from a bicorporeal uterus. A diagnostic accuracy of 55% of differentiation between septate and bicorporeal uterus has been reported in the literature (Reuter et al. (30)). In the study made by Saravelos et al. the sensitivity and specificity of HSG is 78% and 90% respectively, however this examination seems to be poor in differentiating between types of Müllerian duct anomalies. Alborzi et al. reported a sensitivity of 25% in the diagnosis of bicorporeal uterus (31). In addition, Pellerito et al, in an attempt to classify uterine anomalies into different types, HSG was found to be inaccurate in the 20 cases included in the study (32). In contrast, it was considered accurate in diagnosing most DES-related uterine anomalies (Nguyen et al. (33)). Thus, HSG is no longer considered as the "gold standard" in the accurate diagnosis of uterine malformations because of the non-visualization of the uterine myometrium. In our series, the diagnosis accuracy of differentiation between bicorporeal and septate uterus is 55.5%, this same value is reported in the study of Reuter et al.



Graphic 03: Graph comparing the diagnostic accuracy of the type of uterine malformation



Graphic 04: Comparison of sensitivity and specificity of hysterosalpingography.

The sensitivity of HSG in our series is 88.8%, compared to 78% of the mean values of the studies reviewed by Saravelos et al. Thus, the Achille's heel of this diagnostic method is the differentiation between the types of uterine anomalies, which is not negligible given that the management is radically different. However, it remains the first-line examination for the study of tubal permeability in the context of female infertility.



Figure 01: Bilobed appearance of the uterine cavity suggestive of a bicorporeal uterus or a septate uterus.

Radiology Department, Mother and Child Hospital, Hassan II University Hospital, Fez.



Figure 02 : Septate uterus with thin and permeable tubes. Radiology Department, Mother and Child Hospital, Hassan II University Hospital, Fez

## c. Magnetic Resonance Imaging (MRI):

Magnetic resonance imaging offers a noninvasive approach to the evaluation of the uterine cavity and the external contours of the uterus. The criteria used to distinguish bicornuate from septate uterus are often similar to those used on ultrasound. Pellerito et al. reported 100% accuracy (n = 24) in the evaluation of women with surgically proven uterine anomaly; the results were compared with hysteroscopy and laparoscopy (32). Fedele et al. reported 100% sensitivity and 79% specificity in the diagnosis of congenital uterine anomalies (34).

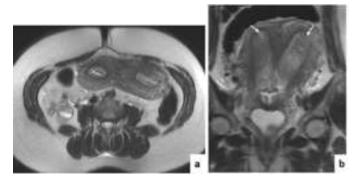


Figure 03 : Pelvic MRI in axial (a) and coronal (b) T2 views showing 02 uterine hemimatrices (white arrows) with a common cervix and surrounded by the serosa in favor of a partial septate uterus. Radiology Department, Mother and Child Hospital, CHU Hassan II, Fez

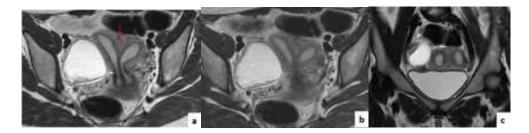


Figure 04: Pelvic MRI in axial T2 (a,b) and coronal T2 (c) views: showing a uterine septum extended to the cervix (white arrow) surrounded by a common serosa (red arrow) in favor of a septate uterus. Radiology Department, Mother and Child Hospital, Hassan II University Hospital, Fez

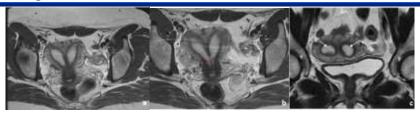
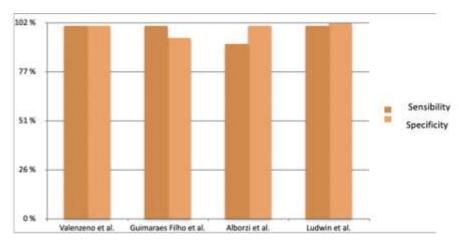


Figure 05: Pelvic MRI in axial (a,b) and sagital (c) T2 views showing 02 uterine hemimatrices (white arrows) with a common cervix (red arrow) and surrounded by serosa in favor of a septate uterus. Radiology Department, Mother and Child Hospital, CHU Hassan II, Fez

In our series, the diagnostic accuracy is 100% in the diagnosis of female genital tract congenital anomalies, the results were compared with the results of hysteroscopy and laparoscopy. The limitation of this examination in the Moroccan socio-economic context is the difficulty of accessibility. Thus, MRI was performed in only 05 patients included in the study.

## d. Hysterosonography (HSG):

Hysterosonography is a radiological technique that allows better visualization of the uterine cavity. Reports comparing HSG with hysteroscopy have suggested that HSG is very accurate in the diagnosis and classification of Müllerian duct anomalies. In the study made by Valenzano et al, hysterosonography demonstrated a sensitivity of 100% and a specificity of 100% (35). In the study made by Guimaraes Filho et al. hysterosonography demonstrated a sensitivity of 100% and a specificity of 94% (36). In the study made by Alborzi et al, hysterosonography showed a sensitivity of 91% and a specificity of 100% (37,38). In Ludwin's 2013 study, 2D hysterosonography showed a sensitivity of 94.3% and a specificity of 83%, 3D hysterosonography showed a sensitivity of 100% and a specificity of 100%. According to the same study, the use of three-dimensional (3-D) ultrasound in combination with hysterosonography provided 100% accuracy compared to laparoscopy/hysteroscopy (8).



Graphic 05: Graph comparing the sensitivity and specificity of hysterosonography in the diagnosis of müllerian duct anomalies according to different studies.

## e. Diagnostic hysteroscopy/ diagnostic laparoscopy:

#### → Hysteroscopy/laparoscopy combination:

Historically, the gold standard diagnostic method for the diagnosis of Müllerian duct anomalies has been laparoscopy combined with hysteroscopy, due to the need for visualization of the uterine cavity and the external contours of the uterus. This diagnostic couple allows to distinguish a septate uterus from a bicornuate uterus.



Figure 06 : Endoscopic image of a septat uterus: U2b C0 V0 . Obstetrics and Gynaecology Department I, Hassan II University Hospital, Fez.



Figure 07 : Fundal incisure of 10 mm in laparoscopy evoking a septate uterus. Department of Gynecology-Obstetrics I, Hassan II University Hospital, Fez.

The diagnosis of certainty is generally made by simultaneous laparoscopy and hysteroscopy. However, less invasive examinations are beginning to compete with this method in terms of diagnosis, in particular 3D hysterosonography, 3D ultrasound and MRI. The high diagnostic accuracy of these radiological examinations questions the need for endoscopy in the diagnosis of Müllerian duct anomalies (8). Hysterosonography, 2D/3D ultrasound and MRI, now allow a precise positive and differential diagnosis without having to admit the patient to the operating room. The development of these diagnostic techniques is imperative for a less invasive but equally precise diagnosis.

## V. Therapeutic management:

The therapeutic management is radically different depending on the type of utero-vaginal malformation.

- 1. Surgical technique:
- a. Septate uterus:

The cure of the uterine septum by surgical hysteroscopy or septoplasty is the rule. Commonly used techniques include transection of the septum using scissors, monopolar or bipolar resector.

Laparoscopy and, more recently, transabdominal ultrasound have been used simultaneously during hysteroscopic incision to confirm the uterine contour, reduce the risk of uterine perforation, and assess complete septal section. Vigoureux et al (2016) (10) published a study concluding that ultrasound guidance during hysteroscopic metroplasty decreased the need for revision. A prospective study by M E Coccia et al (11) comparing the use of ultrasound guidance and laparoscopy during hysteroscopic septal resection showed that ultrasound guidance was comparable to laparoscopy in terms of effectiveness and safety. In the literature, 18 cases of uterine rupture during pregnancy or delivery after septal cure have been reported (12). This risk is linked to excessive resection of the septum, the excessive penetration of the myometrium, perforation of the uterine wall and excessive use of cautery or laser energy during the resection of the septum. In our series, the 13 patients with a septate uterus underwent uterine septum cure by surgical hysteroscopy using a 09 mm diameter hysteroscope with a monopolar resector (T-handle). Guidance of the resection of the septum by trans-abdominal ultrasound or by laparoscopy was not performed.



Figure 08: Uterine septum resection by chirurgical hysteroscopy

Department of gynecology-obstetrics I, Hassan II University Hospital, Fez.

# b. T-shaped dysmorphic uterus:

In our series: 01 patient presented a T-shaped uterus, the patient benefited from an enlargement hysteroplasty.

The resection was performed in the first part of the cycle, using a 9 mm hysteroscope equipped with a monopolar resector. The myometrium was incised laterally on each side, perpendicular to the wall, until a satisfactory size of the cavity was obtained and the 02 ostia of the tubes were visualized.

# c. Bicorporeal uterus:

In our center, patients with the diagnosis of a bicornuate uterus are not treated surgically, therefore the recruitment of patients with this type of malformation was not possible. With the exception of one patient with secondary infertility due to a bicornuate uterus associated with an intracavitary myoma, this patient was included in the study. The procedure performed was a resection of the myoma, otherwise therapeutic abstention was used concerning the uterine malformation.

# d. Vaginal diaphragm or transverse vaginal septum:

The cure of the vaginal diaphragm is a simple technique consisting of resection of the diaphragm in its fibro-conjunctive structure, this procedure is carried out on an annular permeable diaphragm by 2 vertical incisions made from the central orifice, the loss of mucosal substance will have to be compensated for by a submucosal dissection allowing the upstream and downstream mucosal edges to be sutured under tension. Numerous variations have been described, including the Z-plasty: This is an apparently complex technique whose principle is to change the axis of the mucosa-fibroconjunctiva blade of the diaphragm. This transverse axis will be transformed into a vertical axis. In our series, 03 patients included in the study underwent resection of the vaginal diaphragm according to the Z-plasty method described by Garcia.

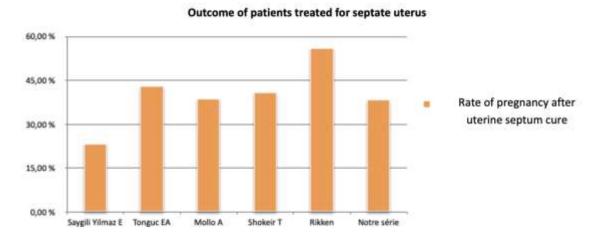
#### VI. Evolution after treatment:

#### 1. Septate uterus

Effect on fertility of hysteroscopic cure of the uterine septum:

Some studies in which infertile women with a septate uterus underwent a septum cure were conducted and the effect on fertility was evaluated. According to the Saygili-Yilmaz E study the cumulative probability of pregnancy was 10% at the first 6 months, 18.1% during the first 6 to 12 months and 23.3% after 18 months (15). The study of Tonguc EA revealed a subsequent pregnancy rate of 43.1% in women who underwent septal cure, which was significantly higher than in women who chose not to undergo surgical cure (20%) (16). Shokeir T's study revealed a pregnancy rate in 41% of women who underwent uterine septum cure (39). However, a study carried out by J.F.W. Rikken et al (2020) (18) did not show any obstetrical benefit compared to the expectant attitude. However, this study presents numerous biases (19). The first bias is that no information is provided on other possible causes of hypofertility in the couple, such as male infertility. The second bias is the large number of centers from which the data were obtained and the long recruitment time included in the study, which gives an average of 0.37 cases/center/year questioning the experience of the operators performing the uterine septum cure. Another bias is a confounding bias due to the inclusion of 19 women (18.4%) who were already pregnant at the time of inclusion in the "expectant" group.

In our series, the evolution of patients with a U2 septate uterus was as follows:



Graphic 05: Graph comparing the evolution of patients with a septate uterus after cure of the uterine septum.

In our series, the pregnancy rate after cure of the uterine septum was 38.4%, which is close to the results reported in the literature. This is a satisfactory result which should encourage the recruitment of patients with a septate uterus. A control hysteroscopy at 08 weeks is desirable, to check that the uterus is healing properly and to free any synechiae.

# 2. T-shaped uterus:

A study published in 2018 by the Strasbourg Medical and Obstetrical Center showed a statistically significant increase in the number of pregnancies (2.5%) vs. 60 (60%), as well as a significant reduction in the number of early abortions, (78.3%) vs. (22%) after enlargement metroplasty in patients with a T-shaped uterus (20).

In another study carried out by Hervé Fernandez (21), concerning 91 patients with hypofertility or infertility with dysmorphic uterus 49.5% of the women became pregnant after enlargement metroplasty. In a study carried out by Di Spiezio Sardo shows an increase in the rate of pregnancies obtained to 57%, an increase in the rate of deliveries to 65%, and an increase in the number of live births to 71% (23). The improvement in fertility is due to better uterine compliance, as well as better vascularization of the uterus (24). In our series, only one patient included in the study had a T-shaped uterus. This patient benefited from an enlargement metroplasty.

# 3. Vaginal diaphragm

For the patients with a vaginal diaphragm, resection of the diaphragm resolved the infertility problem. Thus, the 03 patients who had primary infertility due to a vaginal diaphragm were able to have a successful pregnancy, giving birth to a live child.

# 4. Evolution by age category:

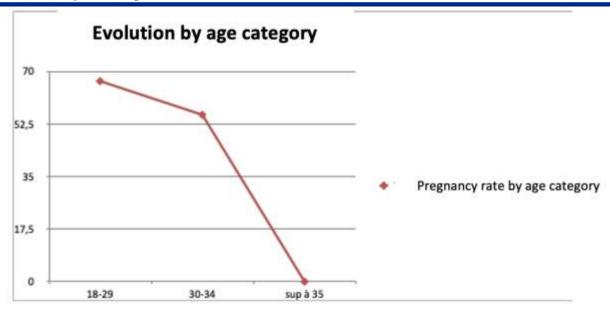


Figure 07: Evolution by age category (our study)

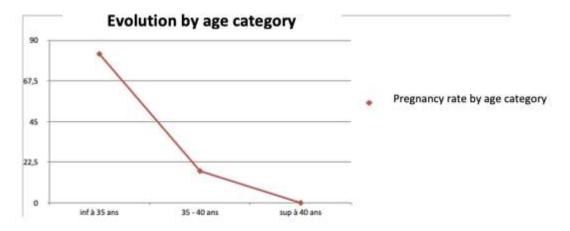


Figure 08: Evolution of patients by age category according to Shokeir T.

In our study, the pregnancy rate in patients under 30 years of age was 66.7%, compared to 55.5% in patients between 30 and 34 years of age. No woman over 35 years of age became pregnant. The pregnancy rate decreased progressively with age, becoming low from the age of 35, which is similar to the results obtained by Shokeir T. in his study (39). This implies that surgical treatment of a genital tract anomalies should be performed at an early age in order to optimize the results in terms of fertility.

In conclusion, genital tract anomalies and fertility is a topical subject because of the curability of these malformations and their accessibility to a less invasive treatment especially with the improvement of endoscopic treatment.

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