11 CONGENITAL MULLERIAN ANOMALIES

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Introduction

Congenital Mullerian anomalies range from uterine and vaginal agenesis to duplication of the uterus and vagina, and also include minor uterine cavity abnormalities somewhere in the range. These are the congenital anomalies that result from arrested development, abnormal formation, or incomplete fusion of the mesonephric ducts.

Uterine congenital anomalies have been related with infertility, recurrent pregnancy loss, prematurity and other obstetric complications which increase perinatal morbidity and mortality rates [1]

Incidence

Columbo reported the first documented case of vaginal agenesis (uterus and vagina) in the 16th century.[2]

The actual incidence and prevalence of mullerian anomalies in the general population are unknown. Non-standardization of classification systems, non-uniform diagnostic modalities, and different study populations of women make reporting of many cases difficult[3].

Incidence rates vary widely and depend on the study. Most authors report incidences of 0.1-3.5%.[4,5]

Prevalance

Reported prevalence rates range from 0.16% to 10% .Overall data suggest that the prevalence both in women with normal fertility and in women with infertility approximates 1%, and the prevalence in women with repeated pregnancy loss approximates 3% [5,6] According to a recent study, women with a history of miscarriage or miscarriage and infertility have higher prevalence of congenital uterine anomalies compared with the unselected population.[26]

Classification[7]

Classification	Clinical Finding	Description
I	Segmental or complete agenesis or hypoplasia	Agenesis and hypoplasia may involve the vagina, cervix, fundus, tubes, or anycombination of these structures. Mayer -Rokitansky-Kuster -Hauser (MRKH) syndrome is the most common example in this category.
II	Unicornuate uterus with or without a rudimentary horn	When an associated horn is present, this class is subdivided into communicating (continuity with the main uterine cavity is evident) and noncommunicating (no continuity with the main uterine cavity). The noncommunicating type is further subdivided on the basis of whether an endometrial cavity is present in the rudimentary horn. These malformations have previously been classified under asymmetric lateral fusion defects. The clinical significance of this classification is that they are invariably accompanied by ipsilateral renal and ureter agenesis.

Congenital Mullerian Anomalies *contd.*

III	Didelphys uterus	Complete or partial duplication of the vagina, cervix, & uterus characterizes this anomaly.
IV	Complete or partial bicornuate uterus	Complete bicornuate uterus is characterized by a uterine septum that extends from the fundus to the cervical os. The partial bicornuate uterus demonstrates a septum, which is located at the fundus. In both variants, thevagina and cervix each have a single chamber.
V	Complete or partial	A complete or partial midline septum is present within a single uterus. septate uterus
VI	Arcuate uterus	A small septate indentation is present at the fundus.
VII	DES-related abnormalities	A *T* -shaped uterine cavity with or without dilated horns is evident.

Mullerian malformations are frequently associated with abnormalities of the renal and axial skeletal systems, and they are often the first feature encountered when patients are initially examined for associated conditions.

Embryology

At 6 weeks of development, the male and female genital systems are similar in appearance, constituting of two sets of paired ducts: the paramesonephric (mullerian) ducts and the mesonephric (wolffian) ducts. In the absence of the Y chromosome, the mesonephric ducts begin to degenerate. The paramesonephric ducts develop along the lateral aspects of the gonads. The proximal segments of the uterovaginal canal remain unfused and open into the peritoneal cavity to form the fallopian tubes. The distal segments progress caudomedially and join each other before contacting the posterior aspect of the pelvic urethra at the level of the sinusal tubercle.[8] These distal segments of the uterovaginal canal give rise to the uterus and upper four-fifths of the vagina. Regression of the uterine septum has been proposed to be a result of apoptosis, mediated by the Bcl2 gene.[9] Absence of this gene has been implicated in persistence of the septum.

At week 12, external uterine contour is fused. Because the fallopian tubes are derived from a different cellular origin than are the uterus and mid- to upper vagina, they are rarely involved in mullerian duct anomalies. During formation of the uterovaginal canal, the sinusal tubercle thickens and forms the sinovaginal bulbs of the primitive urogenital sinus, which gives rise to the lower 20% of the vagina. The uterovaginal canal remains separated from the sinovaginal bulbs by the horizontal vaginal plate. The vaginal plate elongates during the 3rd5th month, and its interface with the urogenital sinus forms the hymen, which usually ruptures during the perinatal period.[10]

Renal agenesis is the most common associated anomaly, although crossed renal ectopy, cystic renal dysplasia, and duplicated collecting systems have all been described .[11]

Diagnosis

1. Hysterosalpingography (HSG): Has its own advantages and disadvantages. It helps us to assess the endometrium and tubal patency but is not able to evaluate the external uterine contour.[12,13]
2. Ultrasound imaging: Hysterosonography, with infusion of saline into the endometrial canal, provides improved delineation of the endometrium and internal uterine morphology. But tubal patency cannot be evaluated. Endovaginal 3D ultrasonography is a non-invasive, outpatient diagnostic modality which enables a detailed assessment of uterine morphology and is superior to other techniques used for the same purpose.[25]

3. Magnetic resonance (MR) imaging has a reported accuracy of up to 100% in the evaluation of mullerian duct anomalies.[14] MR imaging helps us to evaluate internal and external uterine anatomy in multiple imaging planes. MRI is the best imaging method available because of its superior ability to reliably visualize complex uterovaginal anatomy.[24]

Septate Uterus

The septate uterus is the most common mullerian duct anomaly. This anomaly composes approximately 55% of mullerian duct anomalies.[3,15] In this defect the uterovaginal septum fails to resorb partially or completely. The septate uterus is associated with some of the poorest reproductive outcomes. The length of the septum does not appear to correlate with differences in obstetric outcome. Reproductive outcome is known to improve after resection of the septum. In women with septate uterus and a history of infertility, hysteroscopic septoplasty is a safe and effective procedure resulting in a pregnancy rate of 60% and a live birthrate of 45%.[16]

The septum, which arises in the midline fundus, is considered to be complete when it extends to the external cervical os. A partial septum is variable in length.

When evaluating the uterus following hysteroscopic metroplasty, no residual septum or evidence of a residual septum measuring up to 1 cm in length is considered indicative of optimal resection.[17]

Bicornuate Uterus

Bicornuate uterus is the result of incomplete fusion of the uterovaginal horns at the level of the fundus. This defect accounts for approximately 10% of mullerian duct anomalies.[18,3] Patients with a bicornuate uterus usually conceive without treatment provided there are no other extrauterine factors involved in the causation of infertility. Spontaneous abortions and premature deliveries are reported to be higher in women with a complete bicornuate uterus than in those with a partial bicornuate uterus.

Strassman metroplasty has been advocated in women with a history of recurrent pregnancy loss and in whom no other infertility issues have been identified.[19]

Uterus Didelphys

This defect accounts for approximately 5% of mullerian duct anomalies. It results from nearly complete failure of fusion of the mullerian ducts. Each mullerian duct develops its own hemiuterus and cervix and demonstrates normal zonal anatomy with a minor degree of fusion at the level of the cervices. There is no communication between the duplicated endometrial cavities. Spontaneous abortions, premature births are reported. Strassman metroplasty, leaving the duplicated cervix intact in an attempt to prevent cervical incompetence, is a consideration for selected patients with recurrent spontaneous abortions and premature deliveries.[3]

Unicornuate Uterus

When one mullerian duct fails to elongate while the other develops normally results in the unicornuate uterus and accounts for approximately 20% of mullerian duct anomalies. A unicornuate uterus may be isolated, manifesting in 35% of patients. It is usually associated with variable degrees of a rudimentary uterine horn. Common obstetric complications include abnormal fetal lie and intrauterine growth retardation. The cause for spontaneous abortions may be inadequate vascularization and compromised uteroplacental blood flow of the unicornuate uterus. Renal abnormalities are most commonly associated with unicornuate uterus. Renal agenesis is reported in 67% of cases. Ectopic kidney, horseshoe kidney, cystic renal dysplasia, and duplicated collecting systems have also been described .[20]

DES-exposed Uterus

DES is a synthetic estrogen that was introduced in 1948 and prescribed for women experiencing recurrent spontaneous abortions, premature deliveries, and other pregnancy complications. In utero exposure to DES resulted in reduced fertility and increased rates of ectopic pregnancy, spontaneous abortion, and preterm delivery.[21] A T-shaped configuration of the endometrial cavity is the most commonly associated abnormality, seen in 31% of exposed women.[3]

Complex Uterine Anomalies

Mullerian duct development may become arrested at any point in development which results into complex mullerian anomalies which do not fit into any classification. The anomalies include anomalies of the uterine corpus, cervix, and vagina.

Mullerian Agenesis and Hypoplasia

Vaginal agenesis is characterized by an absence or hypoplasia of the uterus, proximal vagina, and, in some cases, the fallopian tubes. Mullerian aplasia is an uncommon, but not rare, anomaly. It occurs in an estimated 1 in 4000 to 10,000 newborn females.[22]

Mayer-Rokitansky-Kuster-Hauser syndrome is the most common manifestation. It results in complete vaginal agenesis, with 90% of cases associated with uterine agenesis. The ovaries are normal in the majority of cases. In approximately 10% of affected women, isolated vaginal agenesis may occur with an obstructed or small rudimentary uterus as a result of failure of development of the sinovaginal bulb.[23]

There is no potential for reproduction in patients with agenesis. In general, little to no reproductive potential is present for patients with hypoplasia, depending on the degree of hypoplasia and the presence of functional endometrium.[3]

Arcuate Uterus

The arcuate uterus is characterized by a mild indentation of the endometrium at the uterine fundus as a result of near complete resorption of the uterovaginal septum. When all extrauterine factors for infertility have been excluded, hysteroscopic correction may be considered in selected patients with recurrent pregnancy loss who have a prominent or broad configuration of the fundal myometrium.

Vaginal Septum and Obstructed Uterovaginal Anomalies

A transverse vaginal septum can be present in any of the mullerian duct anomalies, although it is most frequently seen associated with uterus didelphys and with complex duplication anomalies.

Conclusion

Mullerian duct anomalies are clinically important, especially in women who present with infertility. Precise diagnosis is essential to improve reproductive capability and good obstetric outcome. With the advent of newer surgical modalities, prognosis of patients has changed dramatically.

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12 GENITAL TUBERCULOSIS AND INFERTILITY

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The genital tract plays two roles: reproduction and production of hormones. These hormones act locally to aid in reproduction and peripherally in all parts of the body to help in different functions. Hence, a chronic infection within the reproductive tract of a human can insidiously cause changes in both the anatomy and physiology.

Anatomical distortions caused by tuberculosis are well known and acknowledged. The physiological and immunological changes are still unclear and under study. New diagnostic modalities like PCR, ultrasound, laparoscopy, hysteroscopy and now falloposcopy have enabled the gynaecologist to detect the disease as never before. In the tubes, tuberculosis may cause minimal damage and lead to ectopic pregnancy. This is now demonstrated by falloposcopy. Extensive damage to the tubes can lead to tubal blockage in 60% of cases. Peritubal adhesions and tuboovarian masses have been found in 47.2% of cases. The reproductive outcome in patients of tuberculosis has been described as poor and the results vary from 16- 38.2%. Within the uterus tubercular disease maybe expressed as a mild, moderate or severe form of the disease depending upon the damage to the uterine cavity and the endometrium.

The mild form of disease may not be picked up by clinical symptoms and hysterocscopy but microscopic examination of the endometrium reveals chronic endometritis (fig1) and typical tuberculomas. These tuberculomas represent the host response to the disease and help to contain it. The moderate form may present as caseation (fig.2) pus and adhesion formation. In the severe form the entire cavity is distorted, tubular with dense adhesions and the endometrium is totally disrupted. The patient presents as Ashermann's (fig.3) Syndrome. Antiphoshpholipid antibodies may be found raised in such cases. Wadia [1]has described both laparoscopic and hysteroscopic criteria for the diagnosis of genital tuberculosis (tables 1& 2).

These better detection methods have also enabled us to also ponder over the possibility of latent disease. Why is it that two women harboring tuberculosis behave differently clinically? This is brought about by the intense immunomodulation and the probable physiological changes that the organism brings about even when it lies dormant in the body. As we discover the immunological aspects of latency [2]of this bacterium and its adaptive responses[3], it is realized that fertility can be impaired in tubercular disease even when there is no anatomical damage.

WHO, therefore describes many “states” of tuberculosis which must be recognized and treated accordingly. They are:

Tubercular Disease: Active TB in a case who has never been treated before.

Tubercular infection: MTB present, but not active also called latent infection.

Reactivation of disease: Activation of disease in an individual who has been treated earlier.

Tuberculosis as an Endocrine Disrupter:

Tuberculosis is known to affect the ovaries. Oophritis can cause minute adhesions over the uterine surface causing a disruption of the mechanism of follicular rupture. This leads to LUF. Women with proven genital tuberculosis demonstrate glandular hyperplasia on histopathology because of chronic anovulation[4]. Antigonadotrophic effects of MTB have been demonstrated. Mycobacterium is known to inhibit the basal

production of progesterone and the stimulatory effect of HCG [5]. Hence tuberculosis can cause LPD and lead to failure of implantation. It has also been noted that patients of MTB undergoing IVF exhibit poor ovarian reserve, have high basal levels of FSH, are poor responders and require high doses of gonadotrophins for adequate response. Pregnancy rates are lower and abortion rates higher in such patients[6].

Tuberculosis and immune modulation

Patients with latent tuberculosis carry a very high risk of reactivation whenever their immunity is low. HIV infection has focused attention on the importance of a competent immune system. HIV infections are known to have a low Th_1 response [7]. Hence the balance between Th_1 and Th_2 CD cell lines is reversed favoring activation of MTB. In a recent report [8] it has been indicated that it is the bacillus itself that directs the macrophages and dendritric CD4 cells towards a Th_2 response.

If the immunology of pregnancy is reviewed, a comparison can be drawn with the immuno-compromised HIV patients. For a favorable pregnancy outcome it is essential for the mother to mount a Th_2 response. However, this also favors activation of latent opportunistic infections like tuberculosis. Although there are no randomized control trials in literature to support this hypothesis, some observational studies[9] and case reports[10] indicate that any intervention carried out to achieve a pregnancy can activate a latent tubercular infection and lead to implantation failure or disastrous life threatening results.

Tuberculosis and aPL syndrome:

Transient anti phospholipids are known to be activated in conditions with altered immune response. Tuberculosis is known to alter the immune response and is also accompanied by fibrosis and adhesion formation. This leads to activation of aPL antibodies and micro thrombosis, a known cause of implantation failure in aPL.

Restoring Fertility in Tuberculosis :

There are three forms of treatment :

- Medical management
- Surgical management
- Assisted Reproduction

Medical management forms the mainstay of management since it is important to eradicate the bacterium. The standard WHO regime is followed (table3) for overt disease while single drug regime of rifampicin /INH for 9 months is enough for latent tuberculosis.(table4).

Surgery is indicated in the following conditions :

- Hydrosalpinx and pyosalpinx
- T.O. masses
- Pelvic adhesions and peritonitis
- Ashermann's syndrome.

The results of surgery are not very encouraging with a reported pregnancy rate of 5%.

ART :

The primary indication for ART is pelvic or tubal factor. Additional factors like male factor, age of the female partner are also indications. Most of the published studies are from the west where ART has been performed in established cases of tuberculosis [11,12] hence ovarian reserve was low and results very poor. Indian studies [13,14] on the contrary, recruited patients where genital Koch's was detected on the basis of PCR. These showed a better pregnancy outcome suggesting that if treated early, fertility can be restored.

Authors Experience

All patients complaining of infertility attending our OPD, are screened for tuberculosis if not screened earlier. The diagnosis of Koch's is made if there is one more indicator in addition to a positive PCR. In our analysis of 500 cases, immunology was the next best predictor.All patients are taken up for aggressive management only if the repeat biopsy is negative after medical management. This has given us a very high spontaneous pregnancy rate and an encouraging ART pregnancy rate of 33.5%..

Conclusion

New molecular tests like PCR MTB & BACTEC CULTURE have enabled us to detect the organism in its latent state. Hence we are now gaining insights into the manner in which MTB may bring about physiological and immunological changes and thus cause implantation failure, recurrent pregnancy losses and infertility even in latency. Recognition of the disease when it just begins to effect fertility, gives best results.

TABLE 1

HYSTEROSCOPIC FINDINGS

(1) Microcaseation

(2) Hyperplasia of endometrium with scanty periods (not bleeding to touch with hysteroscope)

(3) Exudation smeared in the uterine cavity

(4) Funnel entrance to tubal ostium is distorted or completely lost

(5) Non-breathing tubal ostium, focusing as a blocked tube

(6) Canalization of ostial area releases flaky caseous material

(7) Hysteroscopic biopsy of sinister part of endometrium gives more positive results

(8) Irregular and ulcerated endocervical canal

(9) Fleshy and hyperplastic cervical erosion not bleeding on touch, and placed anteriorly

(10) Synechiae and fibrosis in the uterine cavity, specially precipitated after a curettage

TABLE 2

LAPAROSCOPIC FINDINGS
(1) High coloured copious peritoneal fluid (tending to become encysted)
(2) Periuteritis (non glistening uterine surface), with lepra patches or a thrush appearance
(3) Blue Uterus on injecting methylene blue
(4) Perisalpingitis, salpingitis Isthmica Nodosa, beaded tubes, rosary appearance, thick tubes, hydrosalpinx
(5) Tubercles, micro & macro caseation (on tube, pouch of Douglas, posterior part of broad ligament)
(6) Flimsy adhesions in right iliac fossa, pouch of Douglas, left iliac fossa, and the liver area
(7) Omental adhesions are fibrous and dense, if formed after surgery
(8) Fibrosis in posterior part of broad ligament, mimicking endometriosis because of breaking of fibrosis typically by ante-verting the uterus
(9) Smaller than normal size fibrous uterus
(10) Synechiae observed by vaginal assistant during elevation of the uterus

TABLE 3

DRUGS FOR TUBERCULOSIS			
Drug	Formulations	Dosage mg/kg/day	Route, Frequency
INH (H)	Tab. 100mg, 300mg Syrup 100mg/5ml	5-10	Oral, Once a day
Rifampicin (R)	Cap 150,300,450,600mg Susp. 100mg/5ml	10	Oral, Once a day Empty Stomach
Pyrazinamide (Z)	Tab. 500,750,1000mg, Syrup 300mg/5ml	25-35	Oral, Once a day
Ethambutol (E)	Tab. 200,400,800,1000mg	20	Oral, Once a day
Streptomycin (S)	Tab. 500mg, 750mg Inj. 1 g vials	20-40	Intramuscular, Once a day

TABLE 4

REGIMES FOR LATENT TUBERCULOSIS
Isoniazid for 9 months
Isoniazid for 6 months
Rifampin and pyrazinamide for 2 months
Rifampin for 4 months

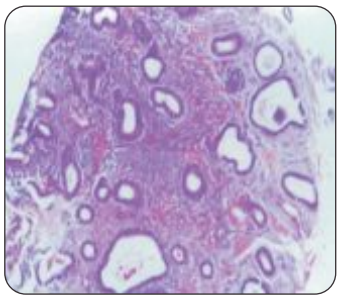

Fig. 1 TUBERCULAR ENDOMETRITIS

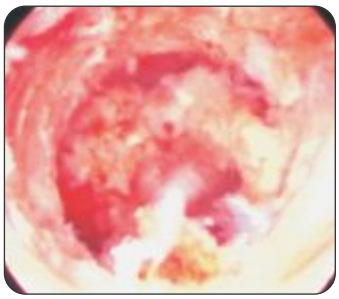

Fig.2 CASEATION: Hysteroscopy

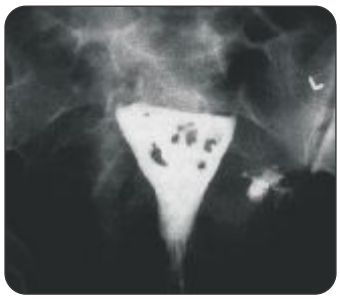

Fig.3 Asherman"s Syndrome

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