REVIEW

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Infantile uterus and uterine hypoplasia: a comprehensive overview to explore possible managements amidst limited scientific certainties

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ABSTRACT

Background: The uterus, a complex organ, performs crucial functions including fertilisation, embryonic implantation, and supporting fetal development. Infantile uterus, resembling a prepubescent girl's uterus, and uterine hypoplasia, characterised by a smaller than normal size but with a normal body/cervix ratio, present significant reproductive challenges.

Objectives: This study aims to critically review the existing literature on the infantile uterus and uterine hypoplasia, focusing on the aetiology, clinical features, diagnosis and treatment options.

Methods: A comprehensive narrative review was conducted based on a thorough database search in PubMed, Google Scholar, Scopus, and Web of Science, complemented by cross-referencing relevant articles. Inclusion criteria included studies on the aetiology, clinical features, diagnosis, and treatment of infantile uterus and uterine hypoplasia.

Main Outcome Measures: Diagnostic criteria based on measurements and therapeutic options.

Results: The review revealed distinct characteristics of infantile uterus and uterine hypoplasia. The infantile uterus has a body/cervix ratio of 1:1 or 1:2, resembling that of a prepubescent girl, while uterine hypoplasia maintains a normal body/cervix ratio of 2:1 but is smaller in size. Diagnostic criteria include a total uterine length of less than 6 cm and specific ultrasound features such as reduced intercornual distance. Therapeutic options include hormonal therapy, particularly oestrogen administration, and surgical interventions aimed at expanding the uterine cavity. Hormonal treatments showed variable effectiveness, primarily beneficial in cases of oestrogen deficiency, while surgical approaches demonstrated some success in enhancing fertility outcomes in women with a hypoplastic uterus.

Conclusions: Infantile uterus and uterine hypoplasia remain poorly understood, with no consensus on their aetiology. Accurate diagnosis relies on specific measurements and body/cervix ratios. Treatment options, including hormonal and surgical interventions, show limited success, indicating a need for further research to optimise management strategies.

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ABSTRACT

What is New? This review highlights the diagnostic challenges and the limited efficacy of current treatments for infantile uterus and uterine hypoplasia, emphasising the need for standardised diagnostic criteria and further research aiming to elucidate more effective therapeutic approaches.

Keywords: Infantile uterus, uterine hypoplasia, congenital uterine anomalies, Mullerian anomalies, infertility

Introduction

The uterus an extremely complex organ, performs crucial functions including facilitating fertilisation, enabling embryonic implantation and hosting the developing product of conception until it reaches a viable state capable of survival in the outside environment. During the normal development of the uterus, significant changes occur in the Müllerian ducts, giving rise to the upper third of the vagina, the cervix, the uterine body, and the Fallopian tubes. However, in certain conditions these changes are incomplete or abnormal, leading to Müllerian malformations that represent a significant category of congenital anomalies of the female reproductive tract, which can substantially impact fertility.[1] These malformations arise from abnormalities in the development of the Müllerian ducts and can range from minor structural defects to significant deformities that severely compromise uterine function.[2] Uterine malformations can impede conception and increase the risk of miscarriage, preterm birth, and other pregnancy complications.[1] Evaluating these anomalies typically involves a combination of imaging techniques, including ultrasound, magnetic resonance imaging, and hysterosalpingography (HSG).[3] Among these, hysteroscopy stands out as a minimally invasive procedure that allows for direct visualisation and treatment of intrauterine abnormalities.[4,5] It not only aids in the accurate diagnosis and classification of uterine malformations but also offers therapeutic interventions that can enhance fertility outcomes.[6,7]

The term "infantile uterus" refers to a uterus resembling the uterus of a pre-menarche girl, exhibiting an absence of changes that occur during pubertal development. Conversely, a hypoplastic uterus has a body/cervix proportion of 2:1, similar to a normal reproductive-aged uterus but overall smaller.[8,9] This narrative review critically analyses the available literature on these enigmatic uterine conditions, exploring their aetiology, clinical features, diagnosis, and therapeutic options.

Methods

This narrative review was conducted through a comprehensive search of multiple databases, including PubMed, Google Scholar, Scopus, Web of Science, and research registers such as Clinicaltrials.gov. The search was complemented by cross-referencing the reference lists of relevant articles. We adhered to the quality standards for narrative reviews as defined and quantified by the Scale for the Assessment of Narrative Review Articles.[10] Keywords used in the search included "infantile uterus", "congenital uterine anomalies", "uterine hypoplasia", and "infertility". The inclusion criteria encompassed original research articles, reviews, and case studies that focused on the aetiology, clinical features, diagnostic criteria, and treatment options for infantile uterus and uterine hypoplasia. Articles lacking a clear focus on these conditions were excluded from the review. Data were meticulously synthesised to provide a comprehensive overview of the current understanding and management of infantile uterus and uterine hypoplasia.

Uterine Development

Understanding the pathogenesis of genital malformations requires considering the embryological origin of various elements of the genitourinary system. During the early stages of embryonic development, significant changes occur in the Müllerian ducts, which differentiate, migrate, fuse, and canalise to form the upper third of the vagina, the cervix, the uterine body, and the Fallopian tubes.[11] By the sixth week of embryonic development, the paramesonephric or Müllerian ducts form, located laterally to the gonadal ridge and the mesonephric ducts. These ducts arise from longitudinal invaginations of the superficial coelomic epithelium, which eventually closes. By the end of the sixth week, both pairs of genital ducts, Wolffian and Müllerian, are present, making the male and female genital systems indistinguishable. The undifferentiated phase of genital development concludes at this point.[12] In the cranial region, the paramesonephric duct presents an open funnel shape, opening into the abdominal cavity. In the caudal

region, it initially moves laterally with the mesonephric duct, crosses it ventrally, and grows in the caudomedially until it meets the opposite paramesonephric duct. Although a septum initially separates these ducts, this septum is subsequently reabsorbed, with the most accepted theory suggesting a cranial direction of reabsorption.[13] An alternative theory, the bidirectional Müllerian theory, suggests bidirectional reabsorption, both cranially and caudally, simultaneously.[14] The caudal tips of the Müllerian ducts project towards the posterior wall of the urogenital sinus, forming a small protrusion called the Müllerian tubercle, which later gives rise to the upper third of the vagina. Each duct consists of three parts: a cranial vertical part opening into the abdominal cavity, a horizontal part crossing the mesonephric duct, and a caudal vertical part that merges with its counterpart on the opposite side. After the descent of the ovaries, the upper two-thirds transform into the Fallopian tubes, while the caudal third fuse to form the uterine cavity, which occurs between weeks 10-12.[15] Following the fusion in the midline of the ducts, a broad transverse pelvic fold, known as the broad ligament of the uterus, forms and extends from the lateral sides of the fused paramesonephric ducts to the pelvic wall. Later, the solid tip of the paramesonephric ducts meets the urogenital sinus.[16] Two theories regarding uterine development are noteworthy. Leyendecker's theory suggests that only the endometrial-subendometrial region and the innermost layer of the uterine body, formed by circular fibres, derive from the Müllerian ducts, referred to as the "Archimetra". The term "neometra" describes the outer layers of the myometrium, which are thought to have a mesenchymal rather than a Müllerian origin.[17] Additionally, experts challenge the classic theory regarding vaginal formation, arguing that the Müllerian ducts do not reach the urogenital sinus. Therefore, the upper third of the vagina does not have a Müllerian origin.[16]

Little is known about the characteristics of the uterus during the early stages of embryonic life. According to O'Rahilly[18], the uterus is indistinguishable as an organ until the 9th week of gestation, and it is only after the 17th week of gestational age that the isthmus, cervix, and the different layers of the uterus can be identified. Novak[19] observed that the fetal uterus in the early stages of development is a tubular structure with a uniform calibre, where marked anteversion or retroversion cannot be appreciated, although a moderate anterior curvature is observed. Additionally, it is almost impossible to identify the uterine body and cervix during early development. The uterus is located above the pubic symphysis, at the abdominal level and above the pelvis.[19] From the 18th week of gestational age, the uterus undergoes linear growth, primarily of the cervix, stimulated by hormones, reaching its maximum development at the end of gestation.[20] Soriano's et al.[21] studies on 140 fetuses showed that the uterus could be measured by ultrasound from the 19th week, with linear continuing until the birth. They determined the width and uterine circumference at different gestational ages, finding that the mean ± standard deviation (SD) of the width and uterine circumference was 12.9 ± 4.1 mm [95% confidence interval (CI) 12.1-13.7] and 40.2 ± 12.5 mm (95% CI 37.9-42.5), respectively. They also established the regression equation for uterine width as a function of gestational age, which was y = 12.9 + 0.73 x gestational age (weeks), where "y" represents fetal uterine width (in mm). For uterine circumference, the regression equation was y = 40.2 + 2.13 x gestational age (weeks), where "y" represents fetal uterine circumference (in mm).[21]

Interestingly, after birth, both the size and volume of the uterus undergo a sudden shrinkage, particularly at the cervix level, due to the hormonal decline experienced by the newborn upon leaving the maternal womb.[22,23] During the infantile phase, the uterus goes through a quiescent stage, with no activity or function, and the body portion of the uterus increases in size, resulting in a 1:1 ratio between the body and cervix. The endometrium is not visible during this stage, although a central echogenic line can be observed on ultrasound.[22,23] During puberty, increased hormone levels lead to significant growth of the uterine body size compared to the cervix, resulting in the typical adult 2:1 body/cervix ratio. There is also an increase in uterine and the organ takes on its characteristic pear-shaped form. The endometrial line becomes visible, and its appearance varies during the menstrual cycle.[22,23]

Researchers have observed variations in uterine size due to physiological and pathological factors. Physiologically, uterine size increases with age and parity, reaching an average length of 7.5 cm by age 40, in the absence of pathologies such as fibroids or adenomyosis. From then on, there is usually a sharp decrease in size starting from menopause due to the decline in hormonal levels until reaching 3 cm again at 90 years of age.[24] Some authors have observed to have a progressive in the thickness of the uterine fundus and the interostial distance with age.[25] The uterus is a dynamic organ subject to changes throughout a woman's life, and its size is influenced by factors such as age, parity, and hormonal status. In

some cases, the uterus does not reach its maximum development or decrease in size compared to the expected age growth curves.[24] These abnormal changes lead to the formation of uteri that are smaller than expected, referred to as hypoplastic uterus and infantile uterus.

Definition

In 1930, Menge and von Oettingen[8] defined hypoplastic uterus and infantile uterus as two distinct conditions characterised by unique morphological and dimensional differences from a normal uterus. These variations are evident in the uterine cavity's size and morphology. The term "infantile uterus" refers to a uterus that resembles that of a pre-menarche woman, exhibiting an absence of the developmental changes that typically occur during puberty. This condition is characterised by a body/cervix proportion of 1:1 or 1:2, resembling that of a prepubescent girl (Figure 1).[8] Conversely, the term "hypoplasia" is derived from the Greek words "hypo", meaning under, and "plasia", meaning formation, defining a uterus that has not reached sufficient development. The hypoplastic uterus has a body/cervix proportion of 2:1, similar to the normal uterus of a woman of reproductive age but is smaller overall (Figure 1).[8] Hegar[26] further refined these definitions by observing uteri of normal size but with an inverted body/cervix proportion. He categorised the infantile uterus into two subtypes: the non-hypoplastic infantile uterus with normal size but an inverted body-to-cervix proportion and the hypoplastic infantile uterus with reduced size along with an inverted body-to-cervix proportion.

To facilitate the diagnosis and classification of different uterine types, Meaker[27] in 1927 introduced the "uterine index". This index determines the proportion between the body and the cervix using a modified and scaled probe. The formula used is 1/2 (U-C/C), where U is the total length of the body plus the cervix, and C is only the cervix measurement. The result for a normal adult uterus is 0.75, while the infantile uterus yields a result of 0.25. Intermediate Values were considered variations of uterine types, with values below 0.60 indicating a degree of hypoplasia.

In 1945, Jeffcoate and Lerer[28] conducted a study involving 120 patients with suspected hypoplastic uteri who underwent uterine length measurement by sound of the cavity under anaesthesia. A uterus measuring over 2 1/2 inches (6.25 cm) was considered normal, while those with a total length below this limit were classified as hypoplastic.[28] In 2002, Barranger et al.[29] defined a hypoplastic uterus as having a reduced cavity size on HSG and a total uterine length not exceeding 6 cm on transvaginal ultrasound in sagittal view (Figure 2).

Currently, there is no consensus on the exact definitions of infantile and hypoplastic uterus. These definitions involve a combination of size and proportions between the uterine body and cervix. Based primarily on Hegar's[26] definitions, a hypoplastic uterus is identified as having a total length of less than 6 cm, whereas an infantile uterus is characterised by a body/cervix proportion of 1:2 or 1:1.

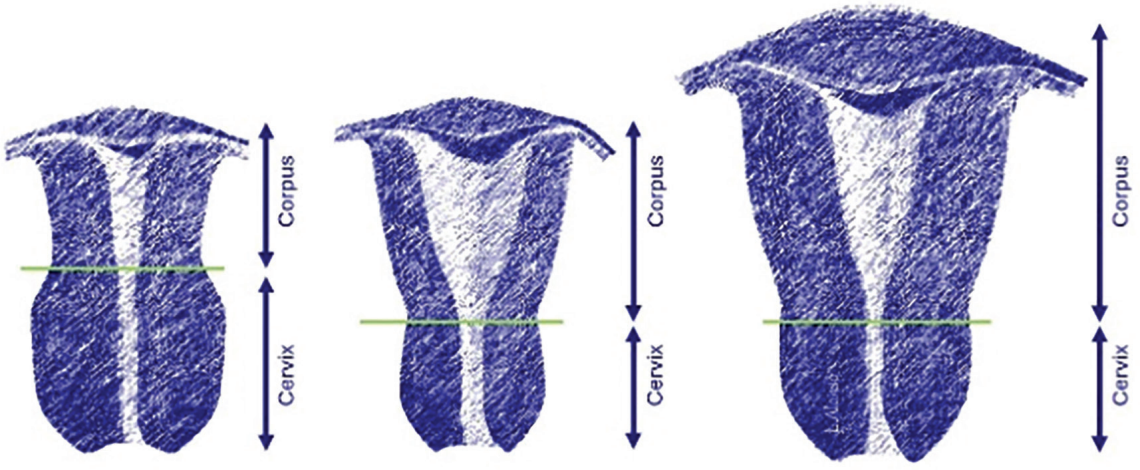

Figure 1. Infantile uterus, hypoplastic uterus, and normal uterus (from left to right). The hypoplastic uterus (centre) displays a body/cervix ratio of 2:1, comparable to that of a normal uterus of a reproductive-age woman (right). In contrast, the infantile uterus (left) has a body/cervix ratio of 1:1 or 1:2, resembling that of a prepubescent girl.

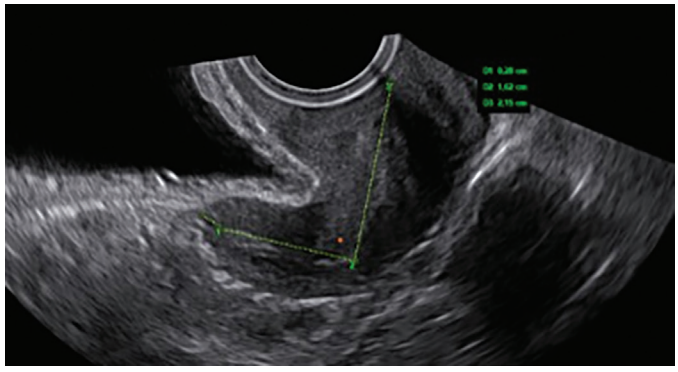

Figure 2. 2D ultrasound view of a hypoplastic uterus. The total uterine length is 4.05 cm, significantly smaller than the normal length of 6 cm.

Aetiology

The aetiology of the infantile uterus and uterine hypoplasia remains largely unknown. Although it is challenging to establish the precise cause of these uterine developmental defects in most cases, it is generally accepted that endocrine failures affecting normal development during adolescence and conditions leading to a deficit in female sex hormones result in delayed uterine development.

In an initial attempt to determine the causes of this condition, Meaker[30] studied a group of 103 women aged 16 to 19 with delayed menarche and genital hypoplasia. Among them, 61 (59.2%) had pituitary insufficiency, 11 had thyroid failure (10.6%), and the remaining 31 (30.2%) had non-endocrine pathologies, with severe anaemia being the most frequent. Subsequently, Jeffcoate and Lerer[28] examined 86 women diagnosed with uterine hypoplasia, defined as having a small uterus with the uterine cavity measuring less than 1 ½ inches. Among these, 21 cases (24.4%) showed no response to oestrogen, as indicated by the absence of bleeding upon oestrogen withdrawal. Another 23 cases (26.7%) had various endocrine dysfunction, including primary hypopituitarism, primary ovarian failure, thyroid dysfunction, and adrenal dysfunction. Additionally, 12 cases (13.9%) combined the two aforementioned causes, while the remaining 10 cases (11.6%) were associated with different diseases such as tuberculosis, severe anaemia, or anorexia nervosa.

It is noteworthy that J. Künzig pointed out a relationship between the presence of a hypoplastic uterus and long-term use of oral contraceptives. To differentiate it from the infantile and hypoplastic uterus, he defined it as a secondary small uterus or "pill uterus".[31] Among well-documented causes, Barranger et al.[29] highlighted in-utero exposure to diethylstilbestrol (DES) as a known cause of hypoplastic uterus. DES, a synthetic oestrogen used to prevent spontaneous abortions, was withdrawn from the market in the 1970s due to health risks, including reproductive tract anomalies in female offspring of exposed mothers. In a series of 29 women diagnosed with hypoplastic uterus, with a uterine length measured by ultrasound less than 6 cm and hysteroscopy revealing a tubular cavity, Barranger et al.[29] reported that 23 (79.3 %) had been exposed in utero to DES.

Turner syndrome (TS) is caused by a total or partial absence of an X chromosome. Characteristics in affected women include short stature, lymphoedema, cervical malformations, and difficulties in sexual character development leading to primary amenorrhoea.[32] According to karyotype, the following types can be observed: 45,X, the most common karyotype, accounting for almost 80% of cases; 45,X/46,XX, a less frequent variant; 45,X/46,iXq; and 45,X/46,XY. According to a study by Doerr et al.[32] of 75 women with TS, only those with TS and a karyotype of 45,X/46,XX had normal uterine sizes, while 26% of those with TS and a karyotype of 45,X had a uterine length <-2 SDS (SD scores), and 18% had a volume <-2 SDS.

Women with Swyer syndrome or 46,XY pure gonadal dysgenesis have a feminine external appearance despite having male sex chromosomes. There is abnormal testicular development associated with a deficiency in the production of male sex hormones. Patients generally have an underdeveloped uterus and fallopian tubes and typically present with primary amenorrhea.[33]

Mayer–Rokitansky–Küster–Hauser syndrome (MRKH) is characterised by typically female secondary sexual characteristics with normal breast development. However, there is a congenital absence of the vagina associated with uterine hypoplasia or aplasia. MRKH affects 1 in 5000 women and is the second most common cause of primary amenorrhea.[34] MRKH is classified into type I (isolated Müllerian defect) and type II when it presents with other associated congenital anomalies such as renal dysplasia, cardiac defects, skeletal system abnormalities, and deafness.[35]

A mutation in the FSH receptor located on chromosome 2p21 (follicle-stimulating hormone receptor) is a rare cause of delayed puberty, amenorrhea, and hypergonadotropic hypogonadism, sometimes associated with the hypoplastic uterus. A case was described of a 19-year-old patient with this mutation, presenting with primary amenorrhea, a hypoplastic uterus, and a very thin endometrial line.[36]

Hyperprolactinemia is a known cause of hypogonadism. When it occurs in adult women, it typically presents with amenorrhea/galactorrhoea. However, when it occurs in pubescent girls, delayed development of secondary sexual characteristics and primary amenorrhea can be observed. It has been documented that the presence of hyperprolactinemia before complete genital development can lead to uterine hypoplasia.[37]

Perrault syndrome is an autosomal recessive disorder characterised by neurosensory hearing loss and ovarian dysgenesis. To date, mutations in six different genes have been associated with this rare disease. Affected women have a normal karyotype (46XX), hypergonadotropic hypogonadism, and typically present with amenorrhea, uterine hypoplasia, and small ovaries.[38]

Clinical Features

Clinical data on the symptoms presented by patients with a small uterus, whether hypoplastic or infantile, are limited. As affirmed by Novak[19] in 1918, the two main functions of the uterus, menstruation and reproduction, are significantly affected by various forms of uterine hypoplasia. Calatroni and Ruiz[39] extensively studied the symptomatology of patients with uterine hypoplasia. They described alterations in vaginal discharge, dyspareunia, menstrual irregularities, infertility, and high rates of pregnancy loss among patients diagnosed with infantile uterus.

Alterations in vaginal discharge can be categorised into two groups: those with normal vaginal discharge and those with scanty discharge, the latter often associated with a deficiency in female sex hormones.[39] Dyspareunia in these patients may be linked to a short or underdeveloped vagina which is smaller than normal, as well as cases of vaginal tightness or a significant decrease in menstrual flow. Regarding menstrual patterns, patients usually experience a decrease in menstrual flow, reaching amenorrhea in severe cases. This reduction in flow may be related to various endocrinopathies or simply because of a smaller endometrial surface area (Figure 3).[39]

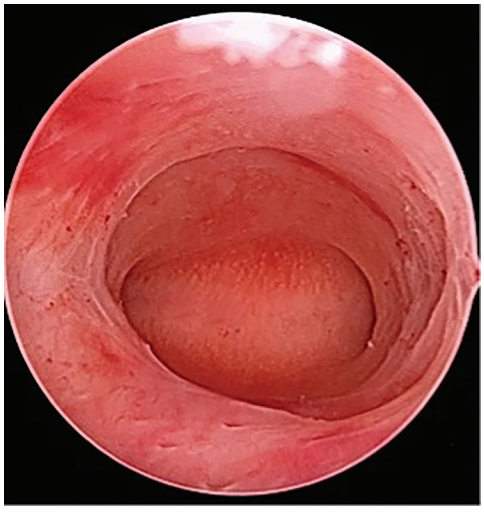

Figure 3. Hysteroscopic view of a hypoplastic uterus showing a significantly reduced cavity size and an exceptionally thin endometrium.

Infertility is common among these patients due to a combination of several factors, including possible associated endocrine alterations that cause uterine hypoplasia, as well as the presence of a nonfunctional endometrium, especially in patients with hypomenorrhoea.[40] Garbin et al.[41] presented a series of 24 women with hypoplastic uterus diagnosed by HSG, of whom 15 had been exposed in utero to DES. Of these, 15 had previous pregnancies with one patient experiencing secondary infertility after a previous full-term pregnancy, and the remaining 14 had a total of 32 pregnancies with no live births. The remaining 9 patients had primary infertility. Subsequently, Barranger et al.[29] presented a study on 29 women with hypoplastic uterus, defined as having a uterine cavity length of less than 6 cm and a tubular-shaped cavity at HSG. Of these patients, 23 had been exposed in utero to DES. Regarding reproductive outcomes, 14 had primary infertility, and the remaining 15 had a total of 26 previous pregnancies, with only one live birth resulting from a premature delivery at 29 weeks of gestation.

Another clinically referred symptom traditionally associated with this type of uterus is spasmodic dysmenorrhoea. Meaker's[30] theory is noteworthy for explaining this phenomenon. Meaker observed that the hypoplastic uterus, similar to the uterus in infancy, contained only 50% of muscle fibres compared to the 90% found in a fully developed adult uterus, with the remaining portion being connective fibrous tissue). This disproportion between muscle fibre and connective tissue is responsible for the presence of irregular and uncoordinated contractions that cause spasmodic dysmenorrhoea.

Diagnosis and Classification

Diagnosing infantile uterus and uterine hypoplasia can be challenging in daily clinical practice due to the limited and often descriptive nature of current classification systems. Among the two most commonly used classifications of uterine malformations, the American Society for

Reproductive Medicine 2021[42] and the European Society for Gynaecological Endoscopy/European Society of Human Reproduction and Embryology (ESGE/ESHRE) 2013, only the latter makes specific reference to the infantile uterus.[43] In the ESGE/ESHRE classification, the infantile uterus is classified as U1b, defined as a uterus characterised by having a narrow cavity, normal thickness of the lateral walls, and an inverted body/cervix correlation, with 2/3 of the total length corresponds to the cervix and 1/3 to the uterine body (Figure 4).

To establish a diagnosis, a high degree of clinical suspicion is essential. Generally, women with delayed menarche, hypo- or amenorrhoea, and reproductive problems such as infertility or recurrent miscarriages should raise suspicion of having a small uterus.[3]

According to Jeffcoate and Lerer[28], the best method to diagnose the presence of a hypoplastic uterus is by measuring its size. However, older diagnostic procedures such as measuring uterine length by bimanual examination or the length of the uterine cavity using a hysterometer, have fallen out of use.

HSG has been frequently used for the diagnosis of these uterine anomalies, yet there are no universally accepted criteria. Hypoplastic or infantile uteri are generally defined as those appearing small on a hysterosalpingogram and often have uterine cavities with T- or Y-shaped morphology.[3]

Hysteroscopy is a minimally invasive technique that allows for the evaluation of the cervical canal and endometrial cavity, aiding in the differential diagnosis of the T-shaped and infantile uterus (Figure 3).[44]

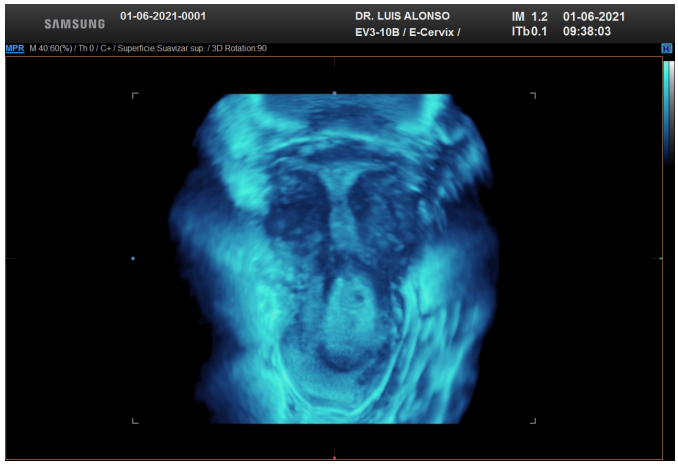

Figure 4. 3D coronal view of an Infantile uterus showing a narrow cavity with normal thickness of the lateral walls and an inverted body/cervix correlation, where 2/3 of the total length corresponds to the cervix and 1/3 to the uterine body.

Using ultrasound criteria, Bonilla-Musoles et al.[45] defined a uterus as hypoplastic or infantile when the measurement from the external cervical os to the fundus of the uterine cavity is less than 6 cm or when the measurement from the external cervical os to the uterine fundus of the uterus (total uterine length) is less than 6.5 cm. Carvalho et al.[46] further attempts to establish more objective criteria, suggesting that a uterus should be considered hypoplastic if the intercornual distance is less than 2 cm or if the distance from the internal cervical os to the uterine fundus is less than 3 to 5 cm (Figure 5). Additional characteristics often present in these uteri include a small cervix, altered uterine anatomy, thickening of the junctional zone, significantly reduced uterine cavity size, and changed uterine blood perfusion diagnosed using Doppler ultrasound.[45]

Currently, there are no universally accepted criteria, but two key criteria are essential for diagnosis: a total uterine length measured from the external cervical os to the uterine fundus of less than 6 cm, as established by different authors over the years based on Jeffcoate's and Lerer[28] clinical results; the body/cervix ratio to differentiate between hypoplasia and infantilism. A ratio of 1:2 or 1:1 identifies an infantile, whereas a hypoplastic uterus maintains a normal ratio of 2:1.

Treatment

Hormonal Therapy

Several treatments have been proposed for patients diagnosed with hypoplastic or infantile uterus. The type of hypoplasia is crucial when choosing the appropriate treatment, necessitating a comprehensive evaluation of

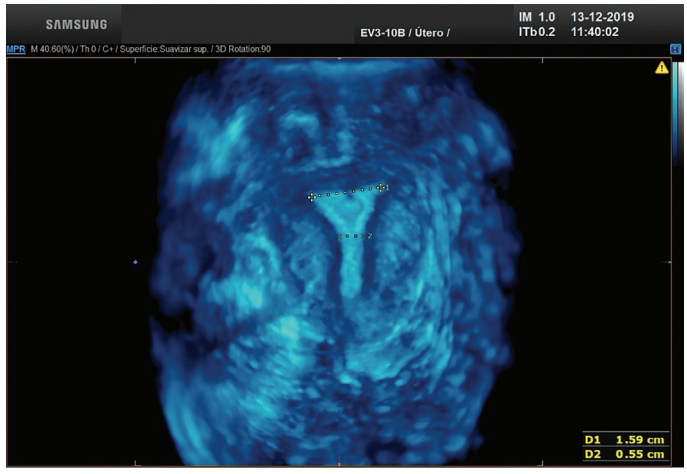

Figure 5. 3D coronal ultrasound view of a hypoplastic uterus, demonstrating a reduced interostial distance of 1.59 cm.

the patient, including hormonal level determination, to ensure an accurate diagnosis and proper treatment.

Given the role of oestrogen in uterine development during puberty, the administration of systemic oestrogens was among the first treatment options explored. In 1934, Clauberg demonstrated increased uterine size through radiological studies, although the effects were temporary.[28] Later, Lardaro[47] presented a series of 30 patients diagnosed with a hypoplastic uterus who received intramuscular stilbestrol, a synthetic oestrogen, at the dose of 5 mg, three times a week for 14 weeks. Uterine growth was observed in only 5 patients; except for two, the growth was temporary. These findings indicate that the effectiveness of oestrogen therapy depends on the uterus's ability to respond, being beneficial primarily in cases where hypoplasia is due to oestrogen deficiency. Local oestrogen injections into the cervix were also explored for many years. In 1955, Field-Richards[48] reported on a preliminary series of 30 patients with hypoplastic uterus treated with cervical injection of oestrogens. Ten milligrams of oestradiol benzoate were injected laterally into the cervical canal, with an average of 4 injections per patient. Uterine growths between 0.4 and 2.2 cm were achieved, with an average increase of 0.94 cm per patient, indicating significant uterine growth in most patients.

De la Puente Lanfranco[49] conducted a notable study on infertile women with uterine hypoplasia diagnosed through HSG. The treatment involved ten injections of 10 mg of oestradiol benzoate to the anterior lip of the cervix, administered over 2 or 3 menstrual cycles. Follow up HSG showed that of the 66 patients who completed the treatment and underwent follow-up, 19 became pregnant (28.7%), 18 normalised the uterine size (27.3%), and 16 showed partial improvement (19.6%), with therapy failing in only 16 cases (24.4%). The authors concluded that this therapy is effective in treating uterine hypoplasia, particularly in cases of primary infertility, minimal uterine hypoplasia, and younger patients.

In 1956, Kaiser[50] proposed creating a pseudo-pregnancy state by pharmacologically prolonging the secretory phase. This therapy, based on oxyprogesterone and oestradiol valerate, was administered to 6 women diagnosed with hypoplastic uterus and dysmenorrhoea. The treatment aimed to extend the secretory phase for two or three weeks and was recommended for cases with a hypoplastic uterus and dysmenorrhoea as well as patients with associated infertility. In 1960, a therapy called "pseudo-pregnancy" was further developed.[51] This approach suggested that similar to the uterus growth observed during pregnancy due to progesterone stimulation, inducing a pseudo-pregnancy state with hormonal therapy could also stimulate uterine growth. The treatment involved an initial dose of estradiol followed by increasing doses of 6-alpha-methyl-17-alfa-hydroxyprogesterone acetate over 4 weeks. The treatment resulted in a measurable increase in uterine size, as evidenced by hysteroscopy and HSG.

Surgical Interventions

Surgical treatment has been documented as an option for patients with hypoplastic or infantile uterus, particularly those experiencing infertility or recurrent miscarriages. Barranger's et al.[29] study highlights the efficacy of such interventions. The surgical technique involves creating two lateral incisions on the uterine walls using a resectoscope loop, approximately 5-7 mm deep, to expand the uterine cavity. Following the surgery, patients received oestrogen-progestagen therapy for two months, followed by a control hysteroscopy. Of the 26 women seeking pregnancy after surgery, 13 (50%) became pregnant, with 9 conceiving spontaneously. These results suggest that expansion surgery, due to its simplicity and minimal post-surgical complications, may be an effective intervention for women with a hypoplastic uterus and a history of recurrent miscarriages and infertility.

Conclusion

Infertile women diagnosed with infantile uterus and uterine hypoplasia represent a significant clinical challenge. Despite extensive research over the past few decades, the aetiology of these conditions remains poorly understood, with various theories proposed but no consensus on the underlying causes. Currently, there are no universally accepted diagnostic criteria. Two critical criteria are important for the diagnosis: a total uterine length measured from the external cervical os to the uterine fundus of less than 6 cm, and the body/cervix ratio, identifying an infantile uterus with a ratio of 1:2 or 1:1, and a hypoplastic uterus with a normal ratio of 2:1. Both medical and surgical treatment have shown limited success, indicating the need for further research to determine the most effective diagnostic and therapeutic approaches for successfully treating female infertility associated with infantile uterus and uterine hypoplasia.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: L.A., J.L.A., Concept: L.A., J.C., Design: M.C., M.C.R., Data Collection or Processing: L.M., J.A.D., E.M., S.S., Analysis or Interpretation: S.G.V., F.P.M., Literature Search: S.G.V., S.S., M.C.R., Writing: L.A., J.C., J.L.A., E.M., F.P.M.

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