

“MÜLLERIAN AGENESIS” EMBRYOLOGIC AND CLINICAL SIGNIFICANCE

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ABSTRACT

Müllerian Agenesis (MA) has been estimated to affect 1 in 4,000 to 5,000 women. Considered to be sporadic, it is a rare congenital disorder of the female reproductive system depicted by the absence of the uterus, cervix and/or upper 1/5th portion of the vagina. Its embryological basis is as a result of failure in the development of the Müllerian (Paramesonephric) ducts and thus, failure of fusion between the Caudal vertical parts of these ducts bilaterally, to form the aforementioned reproductive structures. It has been linked to possible genetic relations, nonetheless, more this article will address in depth the clinical significance and possible causes of this disorder.

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Introduction

Müllerian ducts (Paramesonephric ducts) and Wolffian ducts (Mesonephric ducts) are paired ducts which are the primordia anlage for the maturity of the internal reproductive systems in females and in males correspondingly [1, 30]. They co-exist in the homogenous embryo until they are prompted to differentiate into either ovaries or testes by genetic sex. By the 6th week of gestation, the Müllerian ducts develop lateral to the Wolffian ducts, proliferate and differentiate in a cranial-caudal progression to form the fallopian tubes, the uterus, the uterine cervix and upper 1/5th of the vagina. In contrast, the Wolffian ducts degenerate as a result of the absence of male androgens [2, 31]. In the event where there is failure of the Müllerian ducts to develop properly, Müllerian duct anomalies occur and as a result there is either a total absence or malformation of the female genital structures.

Müllerian Agenesis (MA) is a rare congenital disorder of the female reproductive system [3, 32] which has numerous synonyms, these include the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome or Müllerian Aplasia [3,32]. It occurs due to embryonic growth failure of the paramesonephric ducts resulting in the congenital absence of the upper 1/5th part of the vagina or/and uterus in 90 – 95% of affected patients. It is considered to be a sporadic anomaly but relatively of genetic origin [6, 35] with complications such as Primary Amenorrhea (lack of mensuration due to the absence of the uterus), painful sexual intercourse and the inability of affected patients to carry pregnancies arising later on in life. Nonetheless, patients may be able to have children through assisted reproduction [4, 33, 8, 37]. Although MA is a congenital disorder, it is usually diagnosed in adolescence when the patient presents with

Primary Amenorrhea, one of the most common clinical presentations of MA.

Müller Agenesis is seen to be the second most common cause of Primary Amenorrhea after gonadal agenesis. Women with MRKH syndrome have a female chromosome pattern (46, XX), and as such develop normal secondary sexual characteristics during puberty, their ovaries, given its separate embryological basis, are often normal in structure and function as well as other female external genitalia [4, 33, 5, 34]. Other presenting features of MA include the vaginal canal being absent or marked shortened, a single midline uterine remnant being present or uterine horns with or without an endometrial cavity existing. [8, 37] About 53% of patients with MA/MRKH syndrome are reported to have associated unilateral renal agenesis and skeletal defects. The severity and range of the MRKH syndrome can be subtyped into Type I (Isolated) and Type II (simultaneous with renal, vertebral, auditory and cardiovascular defects in rare cases). Patients diagnosed with MA/MRKH usually undergo psychosocial counselling with fertility and assisted reproductive options being offered to them [5, 34]. There are equally surgical and non-surgical approaches to this congenital disorder. With emphasis on embryological source of origin and possible remedies, this article aims to discuss extensively on Müllerian Agenesis [6, 35, 7, 36, 1, 31].

Incidence

In a general population MA/MRKH has been estimated to affect 1 in 4,000 to 5,000 women [1, 31, 6, 35]. Though majority of MA cases appear to be random, few cases have been found to be inherited (autosomal dominant with an incomplete degree of inherited (autosomal dominant with an

incomplete degree of variable expressivity), proposing that its prevalence is underdiagnosed, making its true frequency in a general population arduous to determine [6, 35, 7, 36].

In the United States, the American College of Obstetrics and Gynecology suggest MA occurs in 1 out of every 4,000 to 10,000 females [5, 34].

Ontogenesis for the normal development of the Paramesonephric Ducts (Müllerian ducts)

The intermediate mesoderm (situated between the paraxial somite forming mesoderm and lateral plate and the cloaca) [11, 40], in a developing embryo ventrally migrates and loses its connection with the somites, thereby forming a longitudinal mass of nephrogenic mesoderm on each side of the body known as the Nephrogenic Cord [11, 40]. The Nephrogenic Cords give rise to longitudinal consensual bulges called urogenital ridges on either sides of the aorta, this formation gives rise to the urogenital system. These ridges, craniocaudally proceed to form three sets of tubular nephric structures, namely, Pronephrons (the cranial most set of tubes), Mesonephrons and Metanephrons (these give rise to adult kidneys). The Mesonephrons located in the midsection of the embryo, form Mesonephric tubules and the Mesonephric ducts (in the case of males). The mesonephric tubules carry out some kidney functions at the initial stage but eventually regress as does many of the tubules, however, its remnants are incorporated into the urogenital system [10, 39, 11, 40]. The gonads (sex organs) arise from the intermediate mesoderm within the urogenital ridges of the embryo. The gonads and reproductive tracts in an embryo are undistinguishable up until the 7th week of embryonic development. The basis to sexual dimorphism is the Y chromosome which contains the testes determining gene known as the SYR gene (sex determining region on Y) [10, 39]. The SYR protein initiates the growth of fundamental sexual organs. Under its influence, male development occurs and in its absence development proceeds along the female path [9, 38].

In the 6th week of intraembryonic life, the Mesonephric ducts and Paramesonephric ducts are both present, however, in the female reproductive system, due to the lack of testosterone production, the absence of Anti Müllerian Hormone (which inhibits the growth of the Müllerian ducts) and the presence of estrogen [10, 39], the Mesonephric ducts begin to regress, thus, the main genital duct in females arise from paired Paramesonephric (Müllerian) ducts [9, 38]. The Paramesonephric (meaning beside the Mesonephric) [13, 42] ducts are formed when the lining epithelium of the Nephrogenic Cords, known as the Coelomic Epithelium, invaginates longitudinally and bilaterally on the anterolateral aspect of the urogenital ridges [9, 38, 10, 39, 11, 40].

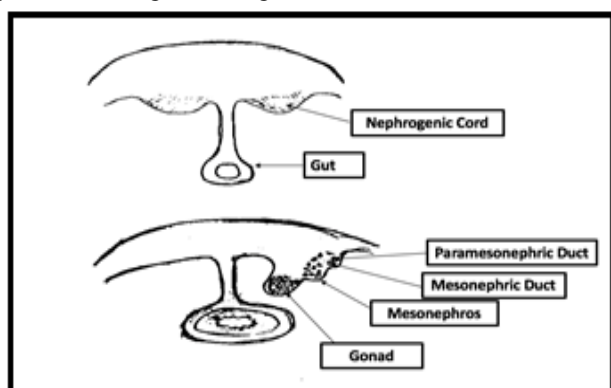


Fig 1. Schematic showing the Nephrogenic cord which gives rise to the urogenital ridges bilaterally.

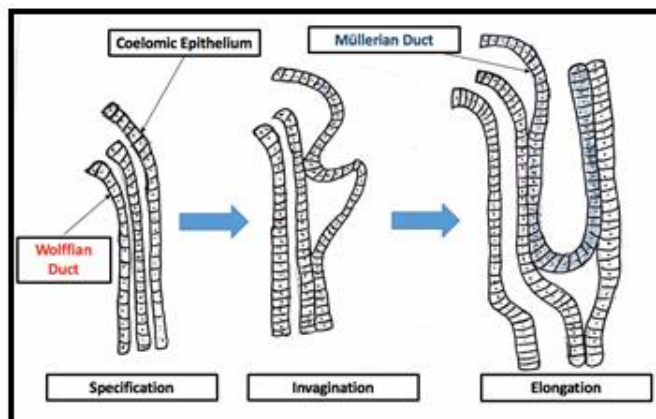


Fig 2. Schematic showing the Coelomic Epithelium and how it invaginates to form the Müllerian Paramesonephric Ducts.

Each Paramesonephric duct can be considered to have three parts, these being, a Cranial Vertical part, a Horizontal part and a Caudal Vertical part. The cranial aspects of the ducts (Cranial Vertical part) open up into the Coelomic cavity with funnel like structures, which will later on form the Fimbriae. They then run ventral and lateral to the Mesonephric ducts and eventually cross the Mesonephric ducts horizontally (the Horizontal Part) to grow in a mediocaudal direction, the horizontal part along with the Cranial Vertical part of the ducts will form the Fallopian/Uterine Tubes bilaterally. Furthermore, fusion between the left and right horizontal parts will form the Fundus of the Uterus [10, 39, 12, 41]. Midline, the Caudal Vertical parts of the ducts come in close contact with each other to fuse. Although they fuse, they are separated by a thin septum known as the Utero Vaginal Septum. This fusion leads to the formation of the Utero Vaginal Canal which would go on to form the Uterus. The fused ducts continue on their path caudally, pushing on the definite urogenital sinus (DUGS) and finally fuse to form the Müllerian/Paramesonephric Tubercle. The Müllerian tubercle forms the cervix of the Uterus as well as the upper 1/5th part of the Vagina [10, 39, 11, 40, 12, 41]. Eventually due to the absence of testosterone, the Mesonephric ducts will totally degenerate.

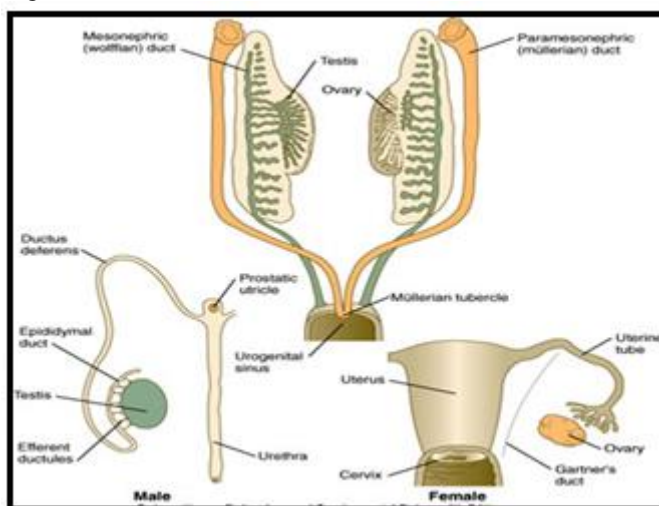


Fig 3. Diagram showing the descent of the Paramesonephric Ducts in Females, parallel to the Mesonephric Ducts, its crossing, continuous descent and eventual fusion to form the Uterus and the Müllerian tubercle which would form the cervix and the upper 1/5th part of the vagina.

Embryological basis for Müllerian Agenesis

Arrests at various morphological stages of the paramesonephric (Müllerian) ducts maturity, precisely in week 7 of embryonic life, are the basis for Müllerian Agenesis. A disruption or dysregulation to the active process of differentiation, migration, canalization and fusion of the paramesonephric ducts [14, 43] will prevent the formation of the respective reproductive structures, giving rise to a wide variety of Müllerian duct anomalies. This halt in the Müllerian ducts development will result in the failure of the horizontal aspects of the ducts, along with the Cranial Vertical part of the ducts to form the Fallopian/Uterine Tubes, subsequently, the Caudal Vertical parts of the ducts will fail to come in close contact with each other and as such, there will be no fusion, leading to the absence of the Uterus. Furthermore, the formation of the Müllerian tubercle [10, 39, 12, 41] would be aborted and as such, there would be an absence of the upper 1/5th of the vagina.

Although the underlying cause of non-formation of the Müllerian ducts are yet to be known, suggestions have been made that Müllerian Agenesis/ MRKH syndrome could be as a result of deficiency of estrogen receptors [15, 44], nonetheless, it's main cause is still classified as idiopathic. Due to the fact that the excretory (Kidneys) and urinary systems develop concomitantly with the reproductive tract [16, 45], Müllerian Agenesis, is usually accompanied by anomalies in these systems such as renal agenesis, horse shoe kidney or fused kidneys [15, 44, 16, 45]. The axial skeletal defects such as scoliosis (abnormal lateral curvature of the spine), which equally accompany the MRKH syndrome are as a result of interruption to the developing mesoderm and its adjacent somites in the embryo.

Classification of Müllerian Agenesis/Mayer-Rokitansky-Küster-Hauser (MRKH)

Patients with this syndrome may present varying signs and symptoms [6, 35], however, these maybe grouped into two different classes, namely, the

I) Typical Type A form.

II) Atypical Type B form [16, 45]

Type A, further known as MRKH Syndrome Type 1 or Isolated Müllerian aplasia (which occurs unaccompanied) is varies in severity between patients and is characterized by failure in the proper development of the Uterus and vagina and thus a congenital absence in both reproductive structures. In certain cases, the uterus and vagina would be absent (aplasia), while in other cases, there would be atresia of the upper 1/5th vagina and a rudimentary uterus [6, 35]. This may also affect the uterine tubes but not the ovaries as these have a varied source of embryological development from the affected organs and as such would function normally. Notwithstanding the fact that patients with MRKH Type 1 experience normal secondary sexual growth characteristics, i.e. normal breast development, hair under the arms and pubic area, increase in fat around the hips and other areas, they still present with primary amenorrhea as an initial symptom. Furthermore, there is still the normal levels of sex steroid and sexual desire (libido), however, patients are unable to bear children due to the underdeveloped uterine tubes and absent uterus. Many patients also experience difficulty and excruciating pain when attempting sexual intercourse as a result of the shortened vagina.

Atypical Type B, also known as MRKH syndrome type II is classified as the simultaneous occurrence of MRKH syndrome type I with additional disorders such as Cervical

Somite Anomalies and Renal dysplasia. The most commonly associated disorder for this type of Müllerian Agenesis are incomplete development of the kidneys, otherwise known as renal dysplasia [6, 16, 35] as well as vertebral malformations. less frequently, they might present with heart malformations and hearing impairment. Patients with MRKH type II [17, 46] may present with absence of a kidney (unilateral renal agenesis), deformity of one or the two kidneys (renal dysplasia), undersized (hypoplastic) kidneys and/or unsuitable positioning within the body of one or both kidneys (ectopic kidneys). Renal abnormalities can result in growth deficiency, kidney stones, an increased predisposition to urinary tract infections and abnormal buildup of urine in the kidneys due to obstruction (hydronephrosis) [6, 35]. Many patients with MRKH syndrome type II also exhibit skeletal malformations. For example, vertebrae bones of the spinal column in the neck (cervical vertebrae) and the upper part of the back (thoracic vertebrae) may mature inadequately (dysplasia). Thus, some of the vertebrae within the neck may be missing and/or fused, causing shortness of the neck, restricted neck movement, and an aberrantly low hairline (Klippel-Feil syndrome). Some affected women may equally have structural abnormalities of the middle ear, causing them to develop hearing loss, due to the failure of sound waves to be conducted through the middle ear. In some cases, the ears maybe malformed, involvement of the ears in the MRKH disorder is referred to as genital renal ear syndrome (GRES) [6, 35, 5, 34].

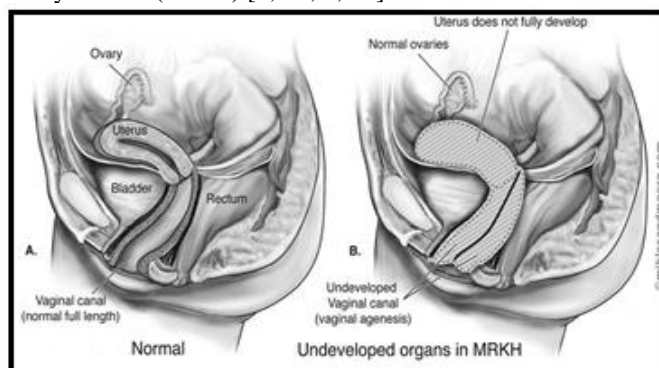


Fig 4. Diagram showing A, the normal development of the female reproductive system and B, abnormal development of the female reproductive system in Müllerian Agenesis. The vagina canal is underdeveloped and the uterus is not fully developed as a result, patients cannot get pregnant.

As earlier mentioned, Müllerian Agenesis/MRKH Syndrome is of an idiopathic cause as, however, fragmentary research suggests various theories to its mechanism. It was thought to occur sporadically as a result of environmental factors or ungenetically related factors (teratogen exposure) which may arrest the normal development of the embryo, nonetheless, no link has been established in this sense [6, 35, 25]. Cumulative evidence suggests that Müllerian Agenesis/MRKH Syndrome maybe genetically related, as some researches have shown the disorder to be an inherited autosomal dominant trait with incomplete penetrance (individuals who inherit the gene for a dominant disorder won't be affected by it) and variable expressivity (the inherited dominant gene for the disorder can present variable signs and symptoms in the affected individual) as genetic diseases are determined by the combination of genes for a particular trait expressed on the chromosomes from both the father and mother. A dominant genetic disease will be expressed only when a single copy of the abnormal gene is necessary for the appearance of the disease.

This abnormal gene can either be inherited from the father or mother or might be as a result of a mutation (gene swap) [1, 30, 6, 35]. Approximately seven deletions and one duplication of chromosomal segments have been recognized in several patients with the MRKH syndrome. These anomalies have been found autonomously in different persons (i.e., one and only one of these chromosomal anomalies per person). These glitches are of varying length and can contain one gene or many different genes. This has allowed researchers to theorize the involvement of certain genes, which are called candidate genes. They are currently working on the characterization of these candidate genes to determine precisely their contribution in the development of Müllerian Agenesis MRKH syndrome [1, 31, 8, 37, 18, 47, 25, 26,27].

With the classical presentation of Primary Amenorrhea which is common in patients with Müllerian Agenesis, further tests to be usually carried out to confirm diagnosis [18]. These can be conducted through laparoscopy (examination of the female pelvic organs) or radiology, diagnostic tests include X-rays, MRI scan, ultrasound and sonohysterography (examining the uterine cavity). Differential diagnosis which is other conditions which present similar signs and symptoms such as Turner syndrome, Androgen insensitive syndrome, Congenital Adrenal hyperplasia and a lot more. The fact that it presents with normal sexual secondary characteristics rules out the possibility of gonadal dysgenesis. Young women diagnosed with Müllerian Agenesis suffer from psychosomatic grief and tremendous apprehension as a result cannot come to terms with the fact that they have no uterus and no or an underdeveloped vagina before any treatment or intervention is proposed, it is essential to manage these patients through psychosocial counselling, so as to address the emotional and functional effects of the disorder [5, 19, 8, 20, 21, 28, 29].

When the patient becomes emotionally stable, surgical methods of approach may be used to remedy this disorder. This includes the correction of the vaginal aplasia by constructing a neovagina. This is where a vaginal canal is surgically created in an adequate size and secretory capacity to enable satisfactory sexual intercourse. The most common method of this procedure would be to dissect a space between the rectum and the bladder, place a split thickness skin graft covered mold in it and diligently use a vaginal dilation postoperatively. The dilation is essential to prevent skin graft contracture. This surgery is usually carried out by an experienced surgeon and is performed in young adulthood (17-21 years) with the consent of patient and parents or guardians, when the patient is old enough to engage in vaginal intercourse and adhere to postoperative dilation [8, 22, 48]. This is to prevent injury to the surrounding tissues and a possibility of a failed outcome post operation.

Discussion

Müllerian agenesis/Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is an erratic congenital disorder which affects women. It is characterized by the absence of the uterus, upper 1/5th of the vagina and underdeveloped or absent uterine tubes in women who have normal ovarian function and normal secondary sexual characteristics. It is as a result of failure in the development of the Müllerian /Paramesonephric ducts which are responsible for the formation of these female reproductive structures. Usually diagnosed in puberty, women with this disorder develop normal secondary sexual characteristics during puberty (e.g., breast development and pubic hair), but lack a menstrual cycle (primary amenorrhea).

Often, the failure to begin the menstrual cycle is the classical clinical presentation of this disorder.

The range and severity of Müllerian Agenesis/Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome can vary significantly and can be classified as either type I, which occurs as an isolated finding, and type II [17, 21, 22, 46, 40], which is accompanied by abnormalities of additional organ systems, mainly the urinary, excretory and the skeletal systems. The particular cause of Müllerian Agenesis remains principally unknown, however, there is now no doubt of a genetic association as updated research information suggests the involvement of several chromosomal segments which include genes that are likely to account for this disorder. Due to its nature, Müllerian Agenesis can cause significant psychological challenges and as such counseling of patients is recommended as the first approach to successfully managing the disorder. A surgical remedy would be creating a neovagina which would enable the patients experience satisfactory sexual intercourse, however, non-surgical procedures for patients who wouldn't want to undergo surgery would be to propose assistive reproductive techniques to them such as the use of in vitro fertilization and a surrogate (gestational carrier) as there is no remedy which could enable patients get pregnant [35, 36].

Conclusion

The inappropriate development of the Müllerian or Paramesonephric ducts in embryonic life can lead to a variety of irregularities in the development of the female reproductive tract, one of which is Müllerian Agenesis. The Incidence of Müllerian Agenesis has most likely been under evaluated primarily because it has, until recently, been seen as a female-specific and sporadic disorder. Isolated features of the triad of main malformations, including kidney agenesis and/or skeletal defects, were consequently not investigated in all probands' relatives. This is comprehensible given the incomplete degree of penetrance, variable expressivity and similarities of this syndrome with other genetic disorders. The construction of a neovagina is offered to patients as a surgical remedy when they are ready to become sexually active and if they are interested. The recent evolution of medical technologies enables patients with this disorder the chance to bypass the absence of inner genital tract and become mothers through in vitro fertilization and surrogate pregnancy and there is a possibility that the number of Müllerian Agenesis patients may increase over time, thus, it is essential to recognize the underlying cause of this disorder or better still, the genetic events which are accountable for it.

References

- [1] Ganesh Elumalai, Sushma Chodisetty. Anomalous "Mutilated Common Trunk" Aortic Arch Embryological Basis and its Clinical Significance. *Texila International Journal of Basic Medical Science*. 2016; 1(1): 1-9.
- [2] Ganesh Elumalai, Emad Abdulrahim Ezzeddin. "The sudden soul reaper" - hypertrophic cardiomyopathy – its embryological basis. *Elixir Embryology*. 2016; 99: 43284-43288.
- [3] Ganesh Elumalai, Muziwandile Bayede Mdletshe. "Arteria lusoria"- aberrant right subclavian artery embryological basis and its clinical significance. *Elixir Embryology*. 2016; 99: 43289-43292.
- [4] Ganesh Elumalai, Sushma Chodisetty, Pavan Kumar D.2016. Ganesh Elumalai et al Classification of Type - I and Type - II "Branching Patterns of the Left Arch Aorta". *Imperial Journal of Interdisciplinary Research*. 2(9): 161-181.

- [5] Ganesh E, Sushma C. The deer horn aortic arches” embryological basis and surgical implications. *Anatomy Journal of Africa*.2016; 5(2): 746 – 759.
- [6] Ganesh Elumalai, Sushma Chodisetty. Teratological Effects of High Dose Progesterone on Neural Tube Development in Chick Embryos. *Elixir Gynaecology*. 2016; 97: 42085-42089.
- [7] Ganesh Elumalai, Sushma Chodisetty. “The True Silent Killers” - Bovine and Truncus Bicaroticus Aortic Arches its Embryological Basis and Surgical Implications. *Elixir Physio. & Anatomy*. 2016; 97: 42246-42252.
- [8] Ganesh Elumalai, Sushma Chodisetty, Bridget Omo Usen and Rozminabanu Daud Patel. “Patent Ductus Caroticus” - Embryological Basis and its Clinical significance. *Elixir Physio. & Anatomy*. 2016; 98: 42439-42442.
- [9] Ganesh Elumalai, Sushma Chodisetty, Eliza Arineta Oudith and Rozminabanu Daud Patel. Common anomalies origin of left vertebral artery and its embryological basis. *Elixir Embryology*. 2016; 99: 43225-43229.
- [10] Ganesh Elumalai, Sushma Chodisetty, Sanjoy Sanyal. Common Nasal Anomalies and Its Implications on Intubation in Head and Neck Surgeries. *Journal of Surgery*. 2016; 4 (4): 81-84.
- [11] Ganesh Elumalai, Malarvani Thangamani, Sanjoy Sanyal, Palani Kanagarajan. Deficient sacral hiatus cause mechanical low back pain: a radiological study. *Int J Anat Res*. 2016; 4(1):1758-64.
- [12] Ganesh Elumalai, Amal Satheesh Sujitha. “Anomalies origin of left coronary artery” its embryological basis and clinical significance. *Elixir Embryology*. 2016; 100: 43446-43449.
- [13] Ganesh Elumalai, Anto Sicily Norbert. “APVC - Anomalies Pulmonary Venous Connections” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43450-43453.
- [14] Ganesh Elumalai, Nnolika Millington. “Coarctation of Aorta” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43425-43428.
- [15] Ganesh Elumalai, Logeshwaran Anbazhagan. “Laryngomalacia” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43420-43424.
- [16] Ganesh Elumalai, Amodini Dharmalingam. “Left superior vena cava” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43429-43432.
- [17] Ganesh Elumalai, Thelma U. Ebami. “Patent Ductus Arteriosus” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43433-43438.
- [18] Ganesh Elumalai, Mouna Arumugam. “Persistent Left superior vena cava” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43454-43457.
- [19] Ganesh Elumalai, Moganelwa Sharline Mampa. “Pulmonary Agenesis” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43439-43441.
- [20] Ganesh Elumalai, Shubham Jain. “Subglottic stenosis” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43458-43461.
- [21] Ganesh Elumalai, Hariharan Arjet. “Tracheoesophageal fistula” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43414-43419.
- [22] Ganesh Elumalai, Jeneffa Princess. “Transposition of Great Vessels” embryological basis and its clinical significance. *Elixir Embryology*. 2016; 100: 43442-43444.
- [23] Ganesh Elumalai, Manoj P Rajarajan. “Type-I vascular rings” Embryological basis and its clinical importance *Elixir Embryology*. 2016; 100: 43700-43705.
- [24] Ganesh Elumalai, Ebenezer Asare Sakyi. “Right sided aortic arch” Embryological basis and its clinical importance *Elixir Embryology*. 2016; 100: 43706-43709.
- [25] Ganesh Elumalai, Enian Senguttuvan. “Double aortic arch” Embryological basis and its clinical importance *Elixir Embryology*. 2016; 100: 43710-43713.
- [26] Ganesh Elumalai, Danesha Sanicharan. “Abnormal origin of the right subclavian artery from the right pulmonary artery” Embryological basis and its clinical importance *Elixir Embryology*. 2016; 100: 43714-43718.
- [27] Ganesh Elumalai, Siva Brinda Jeyapaul. “Choanal Atresia” Embryological basis and its clinical importance *Elixir Embryology*. 2016; 100: 43719-43722.
- [28] Ganesh Elumalai, Kelly Deosaran. “Congenital diaphragmatic hernia” Embryological basis and its clinical importance *Elixir Embryology*. 2016; 100: 43723-43728.
- [29] Ganesh Elumalai, Basim Arif. “Subclavian Steal Syndrome” Embryological basis and its clinical importance *Elixir Embryology*. 2016; 100: 4372943733.
- [30] Guerrier D, Mouchel T, Pasquier L, Pellerin I. The Mayer-Rokitansky-Küster-Hauser syndrome (congenital absence of uterus and vagina) – phenotypic manifestations and genetic approaches. *Journal of Negative Results in BioMedicine*. 2006;5(1).
- [31] Craighill M. Congenital anomalies of the female reproductive tract. *Current Opinion in Obstetrics and Gynecology*. 1993;5(6):758-764.
- [32] Therapeutic S. Müllerian Agenesis | Soul Source [Internet]. Soul Source. 2016 [cited 14 December 2016]. Available from: <http://soulsourcesd.myshopify.com/pages/mullerian-agenesis>
- [33] Reference G. Mayer-Rokitansky-Küster-Hauser syndrome [Internet]. Genetics Home Reference. 2016 [cited 13 December 2016]. Available from: <https://ghr.nlm.nih.gov/condition/mayer-rokitansky-kuster-hauser-syndrome>
- [34] Müllerian Agenesis: Diagnosis, Management, and Treatment - ACOG [Internet]. Acog.org. 2016 [cited 6 December 2016]. Available from: <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Mullerian-Agenesis-Diagnosis-Management-and-Treatment>
- [35] Mayer-Rokitansky-Küster-Hauser Syndrome - NORD (National Organization for Rare Disorders) [Internet]. NORD (National Organization for Rare Disorders). 2016 [cited 5 December 2016]. Available from: <https://rarediseases.org/rare-diseases/mayer-rokitansky-kuster-hauser-syndrome/>
- [36] Patnaik S, Brazile B, Dandolu V, Ryan P, Liao J. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome: A historical perspective. *Gene*. 2015;555(1):33-40.
- [37] Müllerian Agenesis - OBGYN Blog [Internet]. OBGYN Blog. 2016 [cited 6 December 2016]. Available from: <http://www.ijogr.com/blog/2015/mullerian-agenesis/>
- [38] Medicine D. Duke Embryology - Urogenital Development [Internet]. Web.duke.edu. 2016 [cited 6 December 2016]. Available from: <https://web.duke.edu/anatomy/embryology/urogenital/urogenital.html>
- [39] Saddler T. Langman’s Medical Embryology. 13th ed. Wolters Kluwer Health; 2015.

[40]Life Map S. Chapter 91. The Urinary or Excretory System: Intermediate Plate, Nephrogenic Cord, and Pronephros - Review of Medical Embryology Book - LifeMap Discovery [Internet]. Discovery.lifemapsc.com. 2016 [cited 7 December 2016]. Available from: <http://discovery.lifemapsc.com/library/review-of-medical-embryology/chapter-91-the-urinary-or-excretory-system-intermediate-plate-nephrogenic-cord-and-pronephros>

[41]Development of the internal genital organs, indifferent stage [Internet]. Embryology.ch. 2016 [cited 11 December 2016]. Available from: <http://www.embryology.ch/anglais/ugenital/genitinterne01.html>

[42]Uterus Development - Embryology [Internet]. Embryology.med.unsw.edu.au. 2016 [cited 7 December 2016]. Available from: https://embryology.med.unsw.edu.au/embryology/index.php/Uterus_Development

[43]Amesse L, Schmidt C, Lucidi R. Mullerian Duct Anomalies: Overview, Incidence and Prevalence, Embryology [Internet]. Emedicine.medscape.com. 2016 [cited 11 December 2016]. Available from: <http://emedicine.medscape.com/article/273534-overview#a4>

[44]Gupta N P, Ansari M S. Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome - a review. Indian Journal of Urology 2002; 18:111-6

[45]Farooq S. Mayer-Rokitansky-Küster-Hauser syndrome | Radiology Reference Article | Radiopaedia.org [Internet]. Radiopaedia.org. 2016 [cited 13 December 2016]. Available from: <https://radiopaedia.org/articles/mayer-rokitansky-kuster-hauser-syndrome>

[46]Khodry M, Hashim H, Abdelrady A, Hashim A. Unusual form of Mullerian Agensis Syndrome. Middle East Fertility Society Journal. 2014;19(4):329-331.

[47]Mullerian Agensis - Prime Health Channel [Internet]. Prime Health Channel. 2016 [cited 15 December 2016]. Available from: <http://www.primehealthchannel.com/mullerian-agenesis.html>

This Brave Woman Reveals That She Was Born Without A Womb, Cervix, And Vagina [Internet]. EMGN. 2016 [cited 19 December 2016]. Available from: <http://emgn.com/entertainment/brave-woman-reveals-born-without-womb-cervix-vagina/>.